International Journal of Surgery 18 (2015) 163–168

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.journal-surgery.net

Original research

The effects of sulforaphane on the liver and remote organ damage in hepatic ischemia-reperfusion model formed with pringle maneuver in rats

Abdullah Oguz [a,*], Murat Kapan [a], Ibrahim Kaplan [b], Ulas Alabalik [c], Burak Veli Ulger [a], Omer Uslukaya [a], Ahmet Turkoglu [a], Yilmaz Polat [d]

[a] Department of General Surgery, Dicle University Medical Faculty, Diyarbakir, Turkey
[b] Department of Biochemistry, Dicle University Medical Faculty, Diyarbakir, Turkey
[c] Department of Pathology, Dicle University Medical Faculty, Diyarbakir, Turkey
[d] Department of General Surgery, Medical Park Hospital, Elazig, Turkey

HIGHLIGHTS

- Ischemia and reperfusion (I/R) may cause metabolic and structural hepatic injury.
- I/R may occur after trauma, sepsis or hepatic pedicle clamping during liver surgery.
- There isn't an ideal drug preserving the organs from harmful effects of I/R injury.
- In our study, sulforaphane reduced the liver oxidative stress from I/R injury.
- No significant effects of sulforaphane was found on remote organ injuries.

ARTICLE INFO

Article history:
Received 17 July 2014
Received in revised form
9 March 2015
Accepted 21 April 2015
Available online 26 April 2015

Keywords:
Hepatic ischemia-reperfusion
Sulforaphane
Liver
Kidney
Lung
Remote organs

ABSTRACT

Background: The purpose of this study was to investigate the effect of Sulforaphane on ischemia/reperfusion (IR) injury of the liver and distant organs resulting from liver blood flow arrest.
Materials and methods: Fourty Wistar rats were assigned into four groups, each included 10 rats were used. Group I as only laparatomy, Group II laparatomy and Sulforaphane application, Group III hepatic IR; and Group IV as hepatic IR and Sulforaphane application group. Animals were subjected to liver ischemia for 30 min and then reperfusion is started. 5 mg/kg Sulforaphane was applied via oral lavage 15 minutes before initiating the experimental study. Blood samples were taken from the animals for biochemical analysis at 60th minutes of the experiment in the first and second groups; 30 minutes after beginning reperfusion in the third and forth groups. Simultaneously, liver, lung and kidney tissues were sampled for biochemical and histopathological examinations.
Results: The administration of sulforaphane significantly reduced the serum TOA and liver TOA levels, increased the serum TAC and liver TAC levels and also decreased The OSI and liver OSI levels. In the histopathologic examination, the injury was reduced by the administration of sulforaphane. Administration of sulforaphane did not lead to any significant changes in any parameter including histopathological parameters in both the kidney and the lung.
Conclusions: Sulforaphane reduced the liver oxidative stress from I/R injury. A histological injury in liver was reduced by sulforaphane administration. However, there were no significant effects of sulforaphane on the remote organ injuries induced by IR.
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1. Introduction

Ischemia followed by reperfusion (I/R) may cause metabolic and structural hepatic injury and may occur secondary to trauma, sepsis, liver transplantation [1,2], or hepatic pedicle clamping

* Corresponding author. Dicle University Medical Faculty, Department of General Surgery, 21280, Diyarbakir, Turkey.
E-mail address: dragtiz@hotmail.com (A. Oguz).

http://dx.doi.org/10.1016/j.ijsu.2015.04.049
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during liver surgery [2,3]. Although the prevention of hepatic I/R injury has been investigated in many studies, an ideal solution has not been ascertained for preserving the organs from detrimental effects [4,5].

Reactive oxygen radicals, which are released following I/R injury, lead to an inflammatory response and tissue damage by activating chemical mediators. These radicals can also directly damage cellular components [6]. Many studies have shown that the supplementation of free radical scavengers is helpful in reducing tissue damage caused by I/R [7,8].

Sulforaphane is a natural constituent of cruciferous vegetables such as broccoli and cabbage. Studies have demonstrated that sulforaphane exerts antioxidant and anticarcinogenic effects because it induces phase 2 enzymes such as NADPH Quinone reductase and important cellular antioxidants. In addition, it stimulates glutathione reductase and reduces the secretion of several inflammatory cytokines that are associated with bacterial lipopolysaccharides such as iNOS, COX-2 and TNFα. Sulforaphane also has indirect antioxidant effects on the antioxidant system that induces cytoprotective genes and Nrf2-dependent phase 2 enzymes [9–11]. Hu et al. reported that sulforaphane leads to dose-dependent induction of important cellular antioxidants and of phase 2 enzymes including superoxide dismutase (SOD), catalase, the reduced form of glutathione (GSH), glutathione peroxidase, glutathione reductase (GR), and glutathione S-transferase (GST) [12]. Prophylactic therapy with sulforaphane may reduce the oxidative and electrophilic cytotoxicity and the accumulation of free oxygen radicals in the cells [9]. The induction of detoxification enzymes leads to the detoxification and clearance of potential carcinogens and free reactive oxygen radicals that have detrimental and destructive effects on the DNA and on other cells. Sulforaphane is abundant in broccoli and also available as pills with standardized doses. Pharmacokinetic studies have demonstrated that the oral administration of sulforaphane leads to peak plasma concentrations at about 1 h and to a dose-dependent bioavailability of 82%, which decreases at higher doses [13].

It appears from the aforementioned investigations that little attention has been paid to investigate the effectiveness of sulforaphane on minimizing and/or removing the effects of hepatic and remote organ injury induced by hepatic I/R. Although the studies above have examined the effects of sulforaphane on models of brain ischemia and renal ischemia, to the best of our knowledge, no publication is available regarding the models of hepatic ischemia. This was the motivation behind the present study.

2. Materials and methods

2.1. Experimental animals

Forty male Wistar albino rats weighing 250–300 g were randomly selected for our experiment and obtained from Dr. Sabahattin Payzin Health Sciences Application and Research Center, Dicle University. This project was approved by the Committee of Experimental Animals (Dicle University). All experimental procedures were performed as instructed by the Guidelines for the Care and Use of Laboratory Animals. The rats were provided with free access to water and standard rat chow, under 12-h light/dark cycles at 25 °C. All the rats were fasted the night before the operation.

2.2. Surgical procedures and experimental design

Anesthesia was achieved by using 50 mg/kg ketamine hydrochloride (Ketalar, Parke-Davis, Istanbul, Turkey) and 10 mg/kg xylazine (Rompun®; Bayer AG, Leverkusen, Germany) via intramuscular injection and then the experimental procedure was initiated. Solution of 10% povidone-iodine (Betadine®) was used to cleanse the skin. The hepatoduodenal ligament (v. porta, a. hepatica communis and common bile duct) was exposed. After placing a rubber band on top of the hepatoduodenal ligament with 3.0 silk sutures around the turn, the ligament was suspended for 30 min and the period of ischemia was initiated by performing the Pringle maneuver. Following the 30-min ischemic period, the suture was opened by loosening and a 30-min reperfusion period was launched. At the end of this period, the animals were sacrificed by sampling blood from the heart. Animals were grouped as follows:

Group I (Sham): Dissection of hepatoduodenal ligament was performed and no medication was given.
Group II (Control): In addition to dissection, Sulforaphane was given at a dose of 5 mg/kg by oral lavage (according to Tmax) 15 min before the experimental study.
Group III (IR): Thirty minutes after the Pringle maneuver, reperfusion was performed for 30 min and no drug was given.
Group IV (IR + Sulforaphane): In addition to procedures of Group 3, Sulforaphane was given at a dose of 5 mg/kg by oral lavage (according to Tmax) 15 min before the ischemia period.

In each group, blood samples were obtained for biochemical analysis and tissue samples were received for biochemical and histopathological examinations. The liver, both lungs and kidneys were removed and tissue samples were collected. Plasma samples were obtained from blood centrifugation and transferred to plastic Eppendorf tubes for biochemical analysis and stored at −80 °C in a deep freezer. Tissue samples were prepared for biochemical analysis. Foreign tissue residues and blood were removed by flushing with saline and the tissues were transferred to the plastic Eppendorf tubes for biochemical analysis and stored at −80 °C in a freezer. The tissues obtained for histopathological evaluation were placed in plastic containers with 10% formaldehyde solution.

2.3. Biochemical analysis

Total antioxidant capacity (TAC) was performed for each blood sample. Total oxidant status (TOA) and TAC analyses were performed for each tissue sample. In addition, oxidative stress index (OSI) was calculated for each tissue sample.

2.4. Homogenization of tissues

The tissues stored at −80 °C were removed from the freezer and transferred to the laboratory in dry ice. Pieces of 0.30–0.50 g were placed in the tube and 2 ml of Tris–HCl buffer was added. The tissues in the ice-filled plastic containers were processed in the 50 mM pH 7.0 phosphate buffered saline (PBS) for 1–3 min at 14,000 rpm on a homogenizer (UltraTurrax Type T8, IKA Labortechnic, Staufen, Germany). The homogenate was then centrifuged for 30 min at +4 °C. Samples were taken from the supernatant for TOA and TAC analysis.

2.5. TOA analysis

TOA Analysis is a fully automatic colorimetric method developed by Erel [14]. In this analysis, color intensity was measured spectrophotometrically. The TOA values of the tissues were calculated as nmol H_2O_2 equiv./mg protein.

2.6. TAC analysis

This method is a fully automatic method developed by Erel

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