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The Role of Chlorogenic Acid in Alleviating Intestinal Ischemia/Reperfusion-Induced Lung Injury

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Abstract: Here, Chlorogenic acid (CA) was examined in intestinal ischemia reperfusion (I/R)-induced lung injury. 4 experimental rat groups were created (n=8): sham, I/R, I/R+CA 5 mg/kg and I/R+10 mg/kg groups. At the end of the experimental process, rats were immolated and lung tissues were excised. Oxidant parameters increased and antioxidant activity declined in I/R group compared to sham group. CA treatments reversed these parameters. Different doses of the CA prevented intestinal I/R-induced lung injury in experimental animals. © 2020 NTMS.

Keywords: Intestinal Ischemia/Reperfusion, Lung, Chlorogenic Acid, Oxidative Stress, Inflammation, Rat.

1. Introduction

Ischemia is based on the disruption in tissue blood flow which results in cell injury (1). Even though the recovery of blood flow ameliorates the ischemic tissues, reperfusion damages cells through reactive oxygen species (ROS) (2). Ischemia reperfusion (I/R)-induced intestinal injury is a life-threatening health condition which occurs in case of various situations (3). Intestinal I/R injury causes proinflammatory cytokine release, ROS production and oxidative stress (4, 5). Intestinal I/R plays role in distal organ dysfunction development, especially in lungs. Acute lung injury (ALI) is the wide inflammation of lungs and it is a several intestinal I/R injury complication (6-9). ROS induce inflammatory response and inflammation causes more ROS and inflammatory cytokine generation which enhance intestinal injury (10-12). Neutrophils are the main sources for ROS and they play role in reperfusion injury. ROS lead to release of inflammatory cytokines (13, 14) including tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β) (15). IL-1β enhances the production of other inflammatory cytokines and the neutrophil infiltration (16). Total oxidant status (TOS) and total antioxidant status (TAS) act on evaluation of oxidative stress. TAS is the potential of suppressing free radicals (17).

Different agents have been examined to alleviate or eliminate I/R-induced oxidative injuries in various organs (18-22). But the role of Chlorogenic acid (CA) against intestinal I/R injury has not been investigated yet. CA, isolated from Coffea arabica L., performs antioxidant (23) and anti-inflammatory activities (24). CA also demonstrates neuroprotective activity (25, 26).

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Here, it was aimed to find out the effects of CA against intestinal I/R-induced lung injury.

2. Material and Methods

2.1. Ethical Approval, Animals, and Drugs

Atatürk University Experimental Animal Ethics Committee confirmed the study (Protocol No:27.04.2018/102). It was carried out at Experimental Animals Research and Application Center of Atatürk University. The animals were acquired from same center. They were caged with appropriate laboratory conditions and subjected to standard rat feed with tap water. They were deprived of food 12 hours before the experiment, but were free to reach water. Thiopental sodium (Ulagay, İstanbul, Turkey) was preferred for anesthesia. 10% povidone-iodine was used for disinfection and CA was provided by Sigma-Aldrich Co.

2.2. Surgical Procedures and Treatment Groups

32 Wistar Albino male rats, each weighing 230-250 g were used for experimental process. They were held in supine position, shaved, cleaned and applied anesthesia prior to surgical process. They were weighed and divided into 4 groups, including 8 rats in each group (n=8).

Sham group: 1-2 cm size of incision was performed as median laparotomy to abdominal region and then, repaired via 3/0 silk suture.

I/R group: Same steps with sham group were followed. Before suturation, 1-hour ischemia to superior mesenteric artery was carried out through clamping and then, 2 hours reperfusion was carried out as described before (27).

CA 5 mg/kg group: Procedures were done as described in I/R group. 5 mg/kg CA was administered intraperitoneally (i.p.) 30 minutes before the reperfusion.

CA 10 mg/kg group: All steps of CA 5 mg/kg group were carried out but 10 mg/kg CA was administered. CA doses were determined due to a previous I/R study (28). Following the experiment, rats were sacrificed, lung tissue samples were excised and cleaned with normal cold saline.

2.3. Biochemical Examination

Lung tissue samples were homogenized and centrifuged to obtain the supernatants. They were analyzed to determine malondialdehyde (MDA), superoxide dismutase (SOD), myeloperoxidase (MPO), TAS, TOS, TNF-α and IL-1β levels. MDA value was gauged as described previously (29). TAS and TOS levels were determined with appropriate kits (Rel Assay Diagnostics).

Oxidative stress index (OSI) is the ratio of TOS to TAS and measurement MPO activity was measured due to kinetic absorbance as in a former research (31). SOD measurement depends on formazan dye level (32). TNF-α and IL-1β levels were analyzed via appropriate kits (Elabscience, Wuhan, China).

2.4. Statistical Analyses

All data were evaluated through SPSS (version 20.0, for windows). One-way ANOVA test was chosen for data and Tukey HSD test was used for multiple comparisons. Biochemical data results were presented as Mean±Standard Deviation (SD). Statistical significance level was considered when p value below 0.05.

3. Results

Table 1 represents the oxidant and antioxidant biochemical parameters. TAS, SOD values declined significantly in I/R group when compared to sham group, besides TOS, OSI, MDA, MPO levels elevated significantly. CA 5 mg/kg group did not perform a significant change in TAS and SOD values while TOS, OSI, MDA and MPO levels increased. CA 10 mg/kg group was compared with I/R group, all parameters had significant changes except SOD.

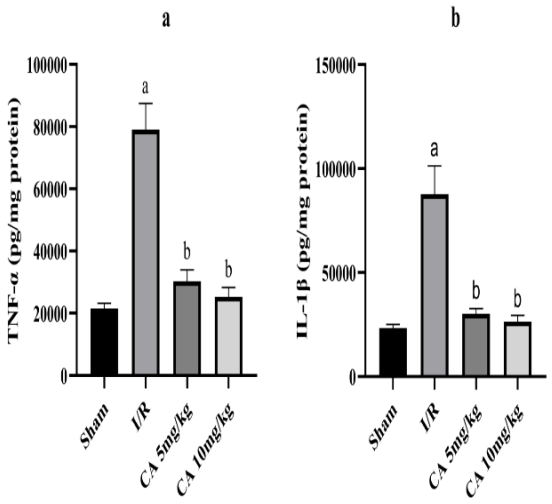

Figure 1: The results of TNF-α and IL-1β levels in intestinal I/R-induced lung injury.

Pro-inflammatory cytokine levels were shown in figure 1a, b. TNF-α and IL-1β levels were found to increase in I/R group compared to sham group. However, it was determined that these levels decreased significantly in CA 5 mg/kg and CA 10 mg/kg groups. In addition, when CA 5 mg/kg and CA 10 mg/kg groups were compared between themselves, TNF-α and IL-1β levels more decreased in CA 10 mg/kg group, but this difference was not statistically significant.

Table 1. The Mean±SD results of biochemical parameters in intestinal I/R-induced lung injury.

Groups (n=8)	TAS (mmol/L)	TOS (µmol/L)	OSI	SOD (U/mg protein)	MPO (U/g protein)	MDA (µmol/g tissue)
Sham	1.16±0.21	8.56±1.28	0.76±0.22	180.66±31.56	326543.23±37695.22	69.27±2.71
I/R	0.79±0.07[a]	12.10±1.62[a]	1.51±0.18[a]	125.88±32.84[c]	475788.57±62770.03[a]	108.46±30.99[a]
CA 5 mg/kg	0.95±0.17	9.30±0.85[b]	1.00±0.24[b]	163.09±27.16	335486.44±23297.06[b]	77.81±13.37[b]
CA10 mg/kg	1.19±0.21[b]	8.70±0.65[b]	0.74±0.08[b]	176.53±54.17	331418.75±68529.04[b]	75.26±8.90[b]

[a]$p<0.001$, [c]$p<0.05$ compared to sham group. [b]$p<0.05$ compared to I/R group.

4. Discussion

I/R is typically composed of blockage in blood flow and following a recovery phase (33). Intestinal mucosa is a vulnerable structure against I/R injury (34). Mesenteric ischemia is an emergency situation characterized with insufficient blood flow resulting from various conditions such as septic shock and surgical interventions (35). Reperfusion is the recovery of blood supply following ischemia. It is required to avoid cell injury and maintain organ functions. Despite all, reperfusion may lead to more damage than ischemia (2, 36). Several health conditions including thrombosis, sepsis, embolism and vasospasm lead to I/R and oxidative stress (37). High morbidity and mortality rates accompany to I/R because it is hard to diagnose and treat (38, 39). I/R may lead to lung injury which enhances morbidity and mortality (40). I/R may lead to ALI in which neutrophil infiltration and proinflammatory cytokine production are typically observed. Even more, ALI may result in acute respiratory distress syndrome (ARDS) and even death. ARDS treatment achieves important improvements but the mortality rate still remains at high levels which creates need to a profound research for underlying mechanisms (41, 42). Ischemia is characterized via decrease or block in blood flow and thus tissues are lack of oxygen and other nutrients. This condition complicates detrimental substance scavenging, particularly ROS (43, 44). ROS proceed from xanthine oxidase activation and play a crucial role in acute intestinal I/R injury (45, 46). ROS production raises in damaged tissues. ROS activate several signaling pathways, induce inflammatory response and injure intestinal during intestinal I/R injury (47, 48).

Intestinal I/R injury is strongly related with oxidative stress. An unbalance between oxygen input and output enhances ROS generation (49) and lipid peroxidation (50). MDA reacts with DNA and proteins resulting damage in intestinal tissues (51). Increase in TNF-α level and neutrophil adhesion capacity accompany I/R injury (52). Proinflammatory mediators including TNF-α and IL-1β play role in neutrophil activation. They also act on enhancing vascular permeability and interstitial edema during I/R injury (53). Active neutrophils secrete MPO which generate free radicals and thus trigger lipid peroxidation (54).

TOS, OSI and TAS values act as oxidative stress indicators and have been used for this purpose in various studies (42, 43). TAS and TOS demonstrate oxidant and antioxidant equilibrium. TAS is an indicator for all antioxidant activity while TOS is limited with ROS (44, 45). SOD catalyzes superoxide free radical conversion into molecular oxygen and superoxide free radical. SOD protects tissues through neutralizing free radicals (46).

Different agents with anti-inflammatory, antioxidant feature and also radical scavengers with beneficial effects have been reported in alleviation or elimination of I/R injuries in various tissues (55-60). In the current study, CA was used for this purpose. CA is a phenol molecule and obtained from various herbs. It performs several properties including antimicrobial activity (61). It is found abundantly in human diet, especially in coffee (62, 63). CA includes R-OH radicals which can inhibit free radical activity through antioxidant activity and thus prevent oxidative cell damage (64). Here, antioxidant and anti-inflammatory effects of CA have been demonstrated in intestinal I/R rat model. SOD activity and TAS value declined while MPO activity, MDA, IL-1β, OSI, TNF-α and TOS levels were elevated in I/R group compared to sham group. CA administration raised antioxidant capacity and diminished oxidant activity by reversing these parameters. Current results enrich the potential CA as to be used in the treatment of I/R related pathologies.

It is necessary to investigate the cellular injury mechanisms to able to improve I/R treatment. Coping with inflammation and oxidative stress contribute to I/R treatment. In this study, oxidative stress and inflammation were diminished via CA.

5. Conclusions

In current research, it has been demonstrated that CA administration declined lung injury caused by intestinal I/R model in experimental rats. Therefore, CA may be a new agent as to be examined against diseases associated with I/R.

Conflict of interest statement

All authors declared that there is no conflict of interest.

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Compliance with ethical standards

The study was carried out in accordance with ethical standards in all aspects.

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