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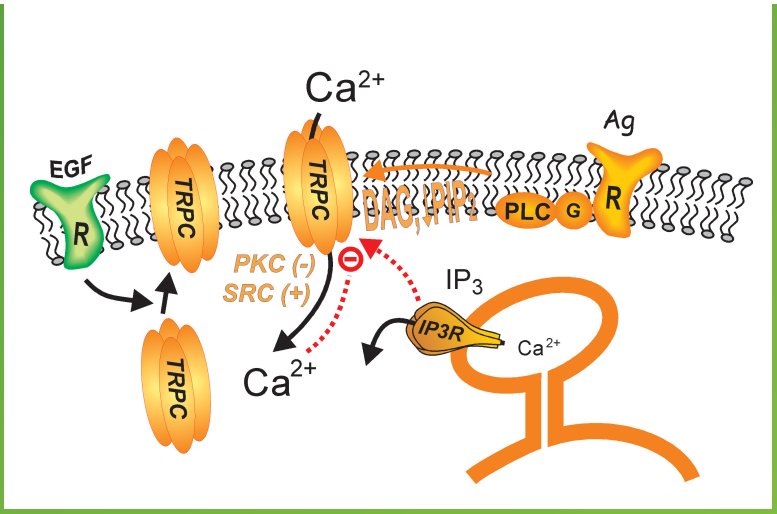

Effects of caffeic acid phenethyl ester and erdosteine on radiocontrast media-induced oxidative stress and histopathological changes in rat testicular tissue

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ABSTRACT

The aim of this study was to determine the possible protective role of caffeic acid phenethyl ester (CAPE) and erdosteine on testicular toxicity of radiocontrast media (RCM) in rats.

A total of thirty-five male Wistar albino rats were included in this study. All animals were equally and randomly divided into four groups as follows: Controls (n=10), RCM-treated (n=8), RCM + erdosteine-treated (n=7) and RCM + CAPE-treated (n=10) groups. RCM was intraperitoneally (i.p.) administered at 10 ml/kg dose. CAPE was administered i.p. at a dose of 10 μmol/kg once daily for two days. Erdosteine was orally administered at 25 mg/kg dose once daily for two days. At the end of the study, all animals were sacrificed. Testis tissues and blood samples were collected for histopathological and biochemical analysis. Catalase (CAT) and superoxide dismutase (SOD) enzyme activity levels and the level of malondialdehyde (MDA) were measured in order to investigate the extent of oxidative stress in testicular tissues. Histopathological examination was also performed on tissue samples stained with hematoxyline-eosin by using light microscope.

In RCM treated group, the mean testicular CAT activity was significantly decreased when compared with the control group ($p < 0.01$). It was observed that the co-administration of CAPE to RCM treated group significantly increased the mean CAT activity in testes tissues when compared with only RCM given group ($p < 0.009$). Co-administration of erdosteine to only RCM given group did not significantly increase the mean CAT activity level in testis tissues when compared with only RCM administered group ($p>0.05$). There was no statistically significant difference between the study group and controls by means of testicular SOD and MDA levels ($p > 0.05$). We have observed that CAPE and erdosteine exhibited protection against RCM-induced toxicity / oxidative stres and histopathological changes in testicular tissues in histopathological aspect.

Taken together, current data suggest that RCM leads to oxidative stress in rat testicular tissues and CAPE may have relatively more protective effect than erdosteine in RCM-induced oxidative stress via antioxidant defence mechanisms.

Key words: Antioxidant enzymes, caffeic acid phenethyl ester, erdosteine, radiocontrast media, testis tissue

INTRODUCTION

Radiographic contrast media (RCM) is a widely used substance in radiologic procedures such as arteriography, venography, intravenous urography, computerized tomography, myelography, interventional cardiology and other examinations (Efstratiadis et al., 2008; ten Dam and Wetzels, 2008) RCM administration may have some severe adverse effects including prolonged hypotension, pulmonary oedema, circulatory collapse, chest pain, angina, myocardial infarction, ventricular fibrillations, cardiac arrhythmias or arrest, convulsions, paralysis, unconsciousness (Katayama et al. 1990; Bush and Swanson, 1991; Hosoya et al., 2000). Some pathological changes induced by contrast medium (epithelial cell vacuolization, interstitial inflammation and cellular necrosis) suggest a direct toxic effect of contrast media on renal tubular epithelial cells (Goldenberg and Matetzky, 2005). In some previous studies, it has been reported that contrast media was found to reduce antioxidant enzymes like catalase and superoxide dismutase in rat renal tissues. Direct cytotoxic effects mediated by reactive oxygen species (ROS) have been observed in canine and rat models of contrast-medium nephropathy (Goldenberd and Matetzky, 2005; Schrader, 2005). Reactive oxygen species (ROS) may play an important role in the pathogenesis of many diseases, particularly in diseases of male and female reproductive system, due to the vulnerability of these organ systems to oxidative stress (Armagan et al., 2008).

Erdosteine (N-(carboxymethylthioacetyl)-homosysteine thiolactone), as a thiol derivate, contains two blocked sulphydryl groups which became free only after hepatic metabolisation. It has two blocked sulphydryl groups that account for the free radical scavenging and antioxidant activity (Dechant and Noble,

1996; Braga et al., 2000). Erdosteine has anti-inflammatory properties and inhibits bacterial adhesiveness (Fadillioglu et al., 2003; Erdogan et al., 2006; Balli et al., 2007). In many studies, erdosteine, an antioxidant, has been sucessfully used as a preventive agent against various toxic agents in animal models and humans (Gazzani et al., 1989; Fadillioglu et al., 2003; Sogut et al., 2004; Sahin et al., 2006; Balli et al., 2007).

Caffeic acid phenethyl ester (CAPE) is an active component of propolis extracts (Sud'ina et al., 1993). It has antiviral (Fesen et al., 1994), anti-carcinogenic (Chen et al., 2001), anti-inflammatory (Michaluart et al., 1999), antioxidant (Sud'ina et al., 1993; Yilmaz et al., 2004, 2005), immunomodulatory (Park et al., 2004), wound-healing accelerating (Koltuksuz et al., 2001), and neuroprotective (Ilhan et al., 2004) properties. At a concentration of 10 □M, it completely blocks the production of reactive oxygen species (ROS) in human neutrophils and the xanthine/xanthine oxidase (XO) system (Sud'ina et al., 1993).

To our knowledge, the possible protective effects of erdosteine and CAPE on RCM-induced possible toxic effects in testes have not been investigated yet. Therefore, the aim of this study was to investigate the possible role of CAT and SOD activities and MDA levels in the pathogenesis of RCM-induced toxicity in testes and to clarify whether there is a preventive role of erdosteine and CAPE on these toxic effects.

MATERIALS AND METHODS

Treatment of animals

Thirty-five healthy male Wistar albino rats, mean weight 242.7±2.13 g were used in the study. Rats were allowed 1 week to acclimate to the surroundings before beginning any experiment. They were housed in cages and kept in an environment of controlled temperature (23±2°C), humidity (60±5%) and photoperiod (12/12h light/dark cycle) for 1 week before initiating the experiment. A commercial balanced diet (Hasyem, Isparta, Turkey) and tap water provided ad libitum. The animals were maintained and used in accordance with the Animal Welfare Act and the Guide for the Care and Use of Laboratory Animals prepared by the Suleyman Demirel University. The animals divided into four groups as follows: control group (n=10), RCM-treated group (n=8), RCM + erdosteine treated (n=7) group, and RCM + CAPE group (n=10). After the 24-h water deprivation period, RCM (meglumin diatrizoat; 370 mg iodine/ml; Urografin®; Schering AG, Germany) was administered intraperitoneally (i.p.) with the dosage of 10 ml/kg for single dose in RCM and RCM+erdosteine, and RCM + CAPE groups. CAPE was administered i.p. with a dose of 10 μmol/kg once daily for 2 days (Yilmaz et al., 2004).

Erdosteine was obtained from a drug company (Ilsan, Istanbul, Turkey), dissolved in distilled water with $NaHCO_3$ and administered orally with the dosage of 25 mg/kg per weight through plastic disposable syringes once daily for 2 days (Özyurt et al., 2004; Öktem et al., 2005). First dose was given 24 h prior to RCM injection. Isotonic saline solution (an equally volume of RCM) was administered to control group by intraperitoneal injection. In addition, $NaHCO_3$ dissolved with distilled water was given orally (as equal volume of erdosteine) to rats in control and RCM groups.

Specimen collection and methods

Rats were anaesthetized with an intramuscular injection of 50 mg kg^{-1} ketamine hydrochloride (Ketalar, Eczacibasi, Istanbul, Turkey) and killed 24 h after the last injection. The testes of rats were quickly removed for biochemical analyses (CAT, SOD, and MDA) and histological evaluation. One of the testes was fixed in 10% formaldehyde for histological examination. The other testis was stored at –20 °C until to the biochemical analyses. The frozen tissue samples of testes were weighed and homogenized in a motor-driven tissue homogenizer (IKA Ultra-Turrax T25 Basic, Germany) with phosphate buffer (pH=7.4). The homogenate was then centrifuged at 5000g-force for 30 minutes to remove debris. The homogenate and supernatant were frozen at –20 °C in aliquots until assayed. The protein content of the tissues was determined using the Lowry method (Lowry et al., 1951)

Determination of lipid peroxidation

Malondialdehyde (MDA) level, an indicator of free radical generation, which increases at the end of LP, was estimated using the double heating method of Draper and Hadley (Draper and Hadley 1990). The principle of the method is the spectrophotometric measurement of the color generated by the reaction of thiobarbituric acid (TBA) with MDA. The concentration of MDA is expressed as nanomoles per gram of protein.

Determination of superoxide dismutase activity

Superoxide dismutase (SOD) activity was determined according to the method of Sun et al. (1988). Activities were expressed in units per milligram protein.

Determination of catalase activity

Catalase (CAT) activity was measured according to the method of Aebi (Aebi 1984). Activities were expressed as k (rate constant) per gram protein.

Histopathological analysis of testes

The testis tissue specimens separated for histopathological examination were fixed in Bouin's solution and then embedded in paraffin. The testis were paraffin-sectioned (5 μm-thick), stained with hematoxylin and eosin (H&E). Histopathological changes on tissue sections were scored according to Cosentino et al. (1986). These changes were graded as follows: Grade I: Showed normal testicular architecture. Grade II: Injuries showed less orderly, noncohesive germinal cells and closely packed seminiferous tubules. Grade III: Injury exhibited disordered, sloughed germinal cells with shrunken, pyknotic nuclei and less distinct seminiferous tubule borders. Grade IV: Injuries defined seminiferous tubules that were packed closely with coagulative necrosis of the germinal cells.

Statistical Analysis

All data are expressed as means $\pm$ S.E. To determine the effect of treatment, data were analyzed using one-way analysis of variance. $p<0.05$ was considered as statistically significant. Significant values were assessed with post hoc multiple comparison tests. Data were analyzed using the SPSS statistical program (version 9.05 software, SPSS Inc. Chicago, IL, USA).

RESULTS

The mean CAT and SOD activities and level of MDA of testes in all four groups are shown in Table 1. In the RCM treated rats, CAT activities in testis tissue were found to be decreased significantly when compared to control rats ($p<0.01$). CAPE co-administration to RCM treated rats, significantly increased CAT activity ($p<0.009$) in testis tissue when compared to rats treated with RCM alone. Erdosteine co-administration to RCM treated rats did not significantly increase CAT activity ($p>0.05$) in testis tissue when compared to rats treated with RCM alone. SOD activities and levels of MDA in the testes were not changed in the study groups compared to control rats ($p>0.05$).

Histopathological findings are summarized in Table 2. Control rats did not show any abnormality for the testis histology (Fig. a). RCM administered Rats clearly showed injury exhibited as disordered, sloughed germinal cells with shrunken, pyknotic nuclei and less distinct seminiferous tubule borders (Fig. b). In contrast, rats in RCM plus CAPE and erdosteine group exhibited mild degrees of these changes (Fig. c,d).

DISCUSSION

Main objective of this study was to investigate the role of oxidative stress to clarify the underlying mechanism of RCM-induced testicular toxicity and to investigate if CAPE and erdosteine restore the toxic effects induced by RCM. To our knowledge, this is the first study considering whether RCM induces oxidative stress and the treatment of CAPE and erdoteine have protective effects in testicular tissue. A study has confirmed the importance of free radical scavengers in modifying sperm function (Jow et al., 1993). We found that the activities of CAT decreased significantly in the testis of the RCM group when compared with the control group. Armagan et al. (2008) found that methotrexate-induced testicular toxicity in the animals is characterized by decreased CAT activity. Yoshioka et al. (1992) reported that RCM reduced the activities of CAT and SOD activities in renal cortex. We found that the treatment of RCM-induced toxicity in rats with CAPE effectively protected the rats against depression-induced testis damage and increased testis CAT activities in testes. Our study demonstrated the protective role of CAPE on oxidative stress. The exact mechanism of CAPE on the antioxidant enzyme activities is not known yet. However, it can be speculated that CAPE may affect the transcriptional and/or translational pathways of these antioxidant enzymes. Another explanation for this effect of CAPE may be that it prevents the induction of antioxidant enzymes by the inhibition of toxic oxidative products (Armagan et al., 2008), which may be related to the antioxidant effect of CAPE.

In the present study, we found that RCM damaged the testes. This injury exhibited that disordered, sloughed germinal cells with shrunken, pyknotic nuclei and less distinct seminiferous tubule borders. CAPE and erdosteine reduced RCM-induced testis damage in rats. CAPE had more protective effective effect according to erdosteine. Spargias et al. (2004) showed that prophylactic oral administration of antioxidant ascorbic acid may protect against contrast-mediated nephropathy in high-risk patients undergoing a coronary procedure. In an animal study by Yenicerioglu et al. (2006), it was suggested that N-acetylcysteine (NAC) protects the kidneys following exposure to contrast medium as it decreased the severity of tubular lesions in rats. NAC, a potent antioxidant, is a thiol-containing radical scavenger and glutathione precursor, is known to reduce oxidative stress (Kaya et al. 2008; Kumar and Sitasawad, 2009). Some experimental studies showed that nebivolol and melatonin have preventive and protective role against the development of contrast-induced nephropathy (Gazi et al., 2006; Toprak et al., 2008). We found that erdosteine co-administration to RCM treated rats did not significantly increase CAT activity in testis tissue when compared to rats treated with RCM alone.

We found that SOD activities and levels of MDA in the testes were not changed in the study groups compared to control rats. Erdosteine did not protect cells against the damage of radiocontrast agents. Similarly, Yenicerioglu et al. (2006) showed that tissue level of MDA was similar in control, contrast, and contrast+NAC groups. In vitro, Garofalo et al. (2007) found that

radiocontrast agents did not increase hydrogen peroxide, superoxide anion or malondialdehyde levels in both tubular cells (LLC-PK1 and MDCK). Additionally, NAC, ascorbic acid, alpha-tocopherol, glutathione, beta-carotene, allopurinol, cimetidine, and citric acid did not protect cells against the damage of radiocontrast agents (Garofalo et al., 2007). Lee et al. (2006) showed that renal SOD activities were not affected after contrast injection. Also, heart tissue was not prone to antioxidant enzyme activities such as glutathione peroxidase and SOD changes after intravenous contrast media injection (Lee et al., 2006).

These results reveal that RCM increases oxidative stress in the rat testes. CAPE and erdosteine have a preventive effect on the oxidative stress via its antioxidant capacity. CAPE seems to have relatively more preventive effect according to erdosteine. However, further molecular and histopathologic studies are needed to elucidate both the exact mechanisms of RCM-induced testis toxicity and protective effect of CAPE and erdosteine.

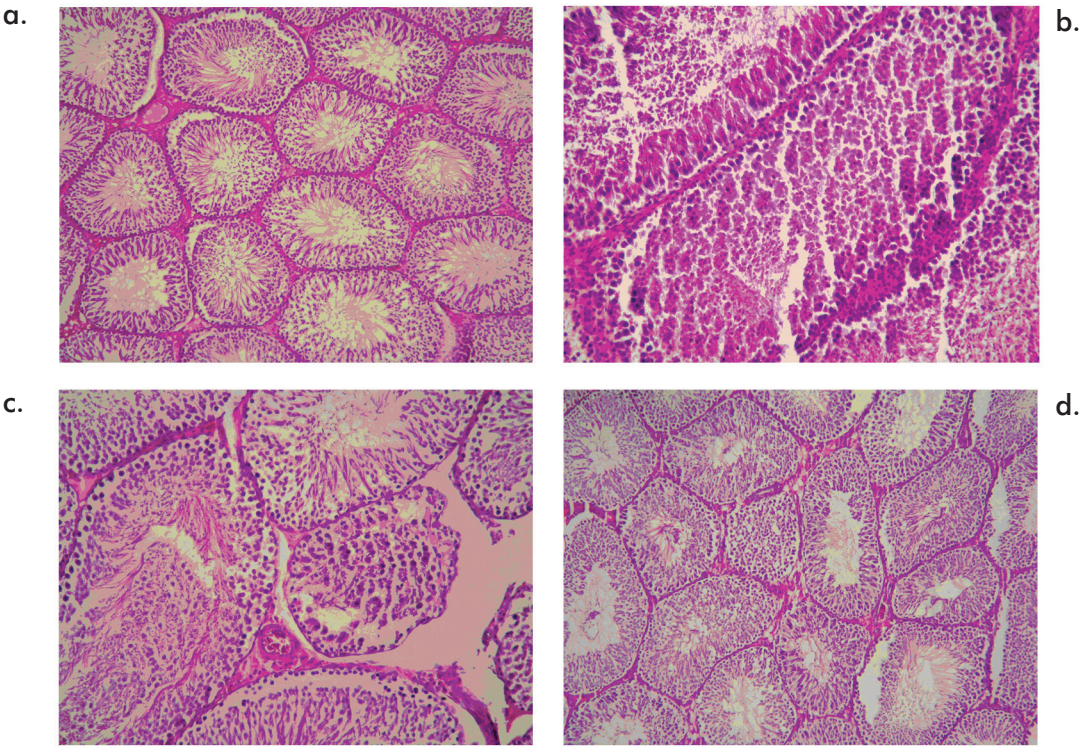
Table 1. The effects of radiocontrast media administration to rats with or without CAPE and erdosteine.

Groups	CAT (k/g protein)	SOD (U/mg protein)	MDA (nmol/g protein)
I- Control (n=10)	0.183 ± 0.010	0.084 ± 0.001	89.36 ± 3.50
II- RCM (n=8)	0.142 ± 0.111	0.077 ± 0.005	91.70 ± 6.18
III - RCM + CAPE (n=10)	0.170 ± 0.011	0.097 ± 0.009	91.18 ± 3.00
IV- RCM + Erdosteine (n=7)	0.166 ± 0.009	0.095 ± 0.012	92.37 ± 4.21
P values			
I-II	0.010	n.s.	n.s.
I-III	n.s.	n.s.	n.s.
I-IV	n.s.	n.s.	n.s.
II-III	0.009	n.s.	n.s.
II-IV	n.s.	n.s.	n.s.

n.s: non significant

Table 2. Histopathological changes in the testes of the study groups.

Groups	Grade mean ± S.E.
I- Control (n=10)	1.000 ± 0.000
II- RCM (n=8)	3.125 ± 0.227
III - RCM + CAPE (n=10)	1.900 ± 0.233
IV- RCM + Erdosteine (n=7)	1.714 ± 0.287
P values	
I-II	0.0001
I-III	0.002
I-IV	0.022
II-III	0.0001
II-IV	0.0001



a. Control group-Grade I: Normal histological structure (H-E x 100).

b. RCM group-Grade IV: Coagulation necrosis was present in germinal cells (H-E x 200).

c. RCM + CAPE group-Grade III: Disorganization and loss in germinal cells (H-E x 100).

d. RCM + Erdosteine group-Grade II: Relatively less disorganized and non-coesive germinal cells (H-E x 100).

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