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Basic Research

Electron microscopic investigation of benzo(a)pyrene-induced alterations in the rat kidney tissue and the protective effects of curcumin

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ABSTRACT

Benzo(a)pyrene (BaP) is a polycyclic hydrocarbon with carcinogenic and DNA damaging properties. Curcumin, primary yellow pigment in turmeric, has a wide range of biological, pharmacological properties in addition to being a powerful

In this article

(10 mg/kg/day), Curcumin (100 mg/kg/day), Curcumin+BaP (100 mg/kg/day+10 mg/kg/day). Agents were daily and orally administered for six weeks. Kidney tissues were removed and examined ultrastructurally. Glomerular and tubular structures in control, corn oil, and DMSO groups demonstrated normal features. Glomerular capillary dilation, thickening, and folding of basement membrane and disruption of organelle contents were distinguished in BaP group. Deletion of podocyte cell and pedicels also sponge-like appearance of glomerular surface were remarkable in this group. Tissue components were protected in curcumin treated group. Proximal tubules and glomerular basement membrane exhibited normal features in Curcumin+BaP group. The abnormalities that accompanied BaP administration clearly revealed the detrimental effects of this agent. Therefore, this study provided substantial evidence that curcumin protects against benzo(a)pyrene nephrotoxicity.

KEYWORDS: Curcumin benzo (a) pyrene kidney nephrotoxicity ultrastructure rat

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Introduction

Polycyclic aromatic hydrocarbons (PAHs) are toxic environmental and chemical contaminants that occur through industrial processes and the combustion of organic materials.[1] They have been implicated in the etiology of a number of diseases, including cancer, through their acute toxic, teratogenic, mutagenic, or carcinogenic effects.[2] Benzo (a) pyrene (BaP) is a well-known PAH compound protype that is formed during high-temperature pyrolytic processes of organic materials such as coal, oil, wood, cigarette smoke, and barbecued meats.[3] Therefore, the compound is pervasive in the environment.[4] Indoor work environments, contaminated air and meals, the burning of animal waste, forest fires, cigarette smoke and, pesticides, are among the main sources of human

level of BaP leads to DNA damage, immunosuppression, toxic effects, and formation of many diseases including cancer in the lung, liver, skin, esophagus, pancreas, colon, stomach, cervix, prostate, and kidney.[6–9] The liver, kidney, hematopoietic, and reproductive systems are reported to display the primary toxic effects of BaP, and chronic exposure of humans to aromatic hydrocarbons is linked to kidney dysfunction and kidney cancer.[9–11]

Plant-based natural components are frequently used as cancer-protective agents due to their high tolerability and low toxicity characteristics. Curcumin, a hydrophobic polyphenol extracted from the roots of the Curcuma longa plant, is the principal yellow pigment in turmeric. It has a vast array of biological and pharmacological effects, as well as antioxidant properties comparable to those of vitamins E and C.[12] One of its primary metabolites, tetrahydrocurcumin (THC), is essential for its biological effects, and curcumin's diferuloylmethane content is responsible for the yellow color of curry.[12,13] In the food industry, curcumin is used as a colorant, preservative, additive, and commonly as a spice. In traditional Asian medicine, the dried roots of the plant have been utilized for therapeutic purposes.[13] Recent studies have demonstrated that it protects against the development of cancer, inflammation, fibrosis, uncontrolled vessel formation, wound healing, lipid metabolism, poisoning, and microbial diseases by decreasing the production of reactive oxygen species and oxidative stress markers.[14–16] Curcumin administration has shown to ameliorate ischemia-reperfusion damage in kidney tissue, reduce diabetic nephropathy symptoms, and improve nephrotoxicity and renal inflammation.[17–19] Hence, curcumin can be utilized as a potential agent for the prevention of kidney-related damage.

However, studies examining the effects of BaP on renal tissue and the potential protective role of curcumin at the ultrastructural level are limited. Therefore, the aim of this study was to investigate the possible protective effects of curcumin

Materials and methods

Animals

Thirty-six male Wistar Albino rats weighting 200–250 g used in this study were supplied by the Gazi University Medical School Experimental Animal Breeding and Experimental Research Center (Ankara, Turkey). Animals were housed in clean, sterile, polypropylene cages with free access to water and standard rat chow. They were kept under standard vivarium conditions with light/dark (12/12 h) cycles, controlled temperature (21–23°C) and humidity. All experimental procedures were performed in accordance with National Institute of Health guidelines for care and the use of laboratory animals and were approved by the Gazi University Local Ethics Committee for Animal Experiments.

Preparation of curcumin and BaP

Curcumin and benzo(a)pyrene (BaP) were purchased from Sigma-Aldrich, USA. Dimethyl sulfoxide (DMSO, Sigma-Aldrich, USA) was used as a curcumin solvent, and corn oil was used as a BaP solvent. Curcumin at a dose of 100 mg/kg/day was prepared by dissolving 0.6 g of curcumin in 15 ml of DMSO, and benzo (a) pyrene at a dose of 10 mg/kg/day was prepared by dissolving 0.06 g BaP in 15 ml of corn oil. Daily, fresh solutions were prepared, and they were preserved in the laboratory at room temperature in the dark. The BaP dose used in this study was selected based on prior research.[20,21]

Experimental design

The 36 rats were randomly divided into six groups (n = 6) as: control, corn oil (1 ml/kg/days), dimethyl sulfoxide (DMSO, 1 ml/kg/day), BaP (10 mg/kg/day), curcumin (100 mg/kg/day), curcumin plus BaP (100 mg/kg/day and 10 mg/kg/day).

of the experimental period.

Transmission electron microscopy (TEM)

Kidney tissues from all groups were dissected into one mm^3 pieces by lancet. Samples were fixed by immersion fixation in 200 mM phosphate buffered 2.5% gluteraldehyde solution (pH 7.4) for 3 hours at 4°C. Samples were then washed with a phosphate-buffered solution and postfixed in 1% osmium tetroxide for one hour at 4°C. Tissues were rinsed again with the same phosphate-buffered solution for three hours, and then they were dehydrated in ascending ethanol series. In order to penetrate the tissues, samples were then placed in a mixture of propylene oxide and araldite plus dodecenyl succinic anhydride (DDSA) for 30 minutes. They were then transferred into the second embedding material (Araldite, DDSA, BDMA (Benzyldimethylamine), DBP (Di-butyl phthalate)) and placed in a rotator at room temperature for two hours, followed by two hours in an incubator at 40°C. Tissues were embedded in the gelatin capsule with secondary material. The araldite blocks were cut into 1 µm thick semi-thin sections with a Leica EM UC7 ultramicrotome (Germany) and stained with toluidine blue. Thick sections were examined by photo-light microscope (DCM 4000, Leica, Germany). Thin sections (0.2–0.5 µm) were placed on copper grids, contrasted with 2% uranyl acetate and lead citrate and grids were examined under a Carl Zeiss EVO LS 10+ ED LaB6 TEM-SEM microscope (Carl Zeiss NTS, Germany). Evaluation of six different cortical kidney tissue areas with renal tubules from all groups was performed using an electron microscope by two blind observers. Tissues were examined for tissue degeneration according to previous study,[22] and changes such as electron-dense intramembraneous deposits (inclusions) in podocyte cytoplasms (EDPC), electron-dense inclusions in mesangial cell cytoplasms (EDMC), pedicel effacement (PE), large vacuole formation (VF), folding of glomerular basement membrane (GBMF) were recorded. A semi-quantitative scoring system (0: no damage, 1: mild, 2: mild to moderate, 3: moderate, 4: moderate to severe, 5: severe) was used to evaluate the severity of the changes in kidney tissue. According to a previous study, all samples from each

each group, and statistical analysis was performed.

Scanning electron microscopy (SEM)

About 1mm^3 dissected kidney tissue was fixed in a phosphate buffered 2.5% gluteraldehyde solution (pH 7.4) for 4 hours at 4°C. Samples were dehydrated via an ascending degree of acetone. Tissues were dried with a critical point dryer (Leica EM CPD030, Germany) and dehydration was completed. After this step, each sample was adhered to the aluminum transport chambers with liquid silver, and they were coated with gold palladium (AuPd) in a coating device (LLC Desk V Sputter/etch unit, Denton Vacuum, USA). Tissues were inserted into Carl Zeiss EVO LS 10 LaB6 TEM-SEM microscope holders and examined and photographed using a SEM microscope at a 10kV acceleration voltage. Six cortical kidney samples were investigated from each group, and changes such as pedicel effacement (PE), distortion of podocyte cell morphology (PCD), and distortion of primary and secondary podocyte cell processes (PSPD) were noted. A semi-quantitative scoring system (0: no damage to 5: severe) was used to evaluate the severity of the changes. All samples from each group were evaluated under an electron microscope in one central and five peripheral areas and six numerical values were obtained for each animal in six areas.[23] The average of the scores was calculated, and statistical analysis was performed.

Statistical analysis

The values for the mean and standard deviation were determined for presenting the data. Kruskal–Wallis H test was used to compare the groups according to each variable. When significant results were obtained from the Kruskal–Wallis test, Bonferroni's adjusted Mann–Whitney U test was performed for pairwise comparisons. Data analysis was performed with Statistical Package for Social Sciences (SPSS) software version 15.0 (SPSS Inc., Chicago, IL) and $p < .05$ was considered statistically significant.

Normal ultrastructure of podocytes, mesangial cells, endothelial cells, endothelial cell fenestrations, secondary foot processes (pedicels), urinary space, and GBM in the kidney glomerulus were observed in the control group (Figure 1A). Tubules from the same group revealed obstructed lumen due to long brush border microvilli. Basal foldings in proximal tubule cells and parallelly located mitochondria were clearly distinguished. Normal histological structures such as large and small lysosomes, all cell organelles, and euchromatic round cell nuclei and nucleoli were seen in the cytoplasm (Figure 2A). Corn oil and DMSO administered groups exhibited normal glomerular (Figure 1B, C) and tubular (Figure 2B, C) structures similar to the control group. Glomerular capillaries in the BaP group were enlarged, the basement membrane was irregularly thickened and folded, podocyte cell nuclei were heterochromatic, and the cytoplasmic appearance was electron-dense, slightly swollen, and degraded. Podocyte processes revealed irregular and blunt structures, and secondary foot processes disappeared and effaced in some areas. In addition to pedicel effacement, the presence of intramembranous electron dense inclusions in the podocyte cytoplasm and electron-dense inclusions in mesangial cell cytoplasm were also detected. In certain mesangial cells, the nucleus was heterochromatic, and there was extensive lipid deposition in the cytoplasm. In addition, disruption of organelle contents as well as microvilli, and vacuole-like structures in the cytoplasm of all cell types were distinguished (Figure 1D). The nuclear heterochromatin was intense in tubule cells compared to control. Basal foldings disappeared locally, and basal mitochondria became rounded and dispersed throughout the cytoplasm. It was also determined that certain lysosomes in the cells merged to form irregular lysosomal structures, and the tubular basement membrane thickened (Figure 2D). In the curcumin group, all components of the glomeruli (Figure 1E) and tubules (Figure 2E) were distinguished by a normal structure similar to the control. In the curcumin plus BaP group, heterochromaticity persisted, whereas the basement membrane was recovered to its normal structure, remaining structures were intact

Figure 1. Transmission electron microscopic (TEM) images of kidney glomerulus. Control (**a**), Corn oil (**b**) and DMSO (**c**) groups showing intact glomerular structure with capillaries (K), endothelial cells (E), endothelial cell fenestrations (⇉), mesangial cells (M), podocytes (P), secondary foot processes (→), urinary space (⇦) and glomerular basement membrane (*) . BaP (**d**) group showing prominent vacuoles (V), electron-dense inclusion deposits in mesengial cell cytoplasms (+) and electron-dense intramembraneous inclusions in podocyte cytoplasms (++). Curcumin (**e**) group demonstrating glomerulus with normal appearance. Endothelial cell, endothelial cell fenestrations, mesangial cell, secondary foot processes and glomerular basement membrane are seen in Curcumin plus BaP (**f**) group (Uranyl acetate, lead citrate, scale bars: 2 µm).



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nucleolus (⋆) and tubular basement membrane (BM). BaP (**d**) group showing brush border microvilli, lysosomes, mitochondria, cell nucleus and basal foldings. Curcumin (**e**) group demonstrating glomerulus with normal appearance. Brush border microvilli, lysosomes, mitochondria, cell nucleus, basal foldings and tubular basement membrane are seen in Curcumin plus BaP (**f**) treated group (Uranyl acetate, lead citrate, scale bars: 2 µm).



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Statistical analyses of TEM degenerations indicated that the lowest EDPC was observed in the control group, and it was similar ($p = .555$) to corn oil and DMSO groups. The EDPC degeneration in curcumin and curcumin plus Bap were similar ($p > .05$) to the control group and to each other. The EDPC in the corn oil and DMSO

groups. EDCM levels in these groups were similar ($p > .05$) to each other. The lowest PE observed in control and curcumin groups and there was statistical similarity ($p > .05$). PE in corn oil group was similar ($P = .317$) to the control and curcumin groups, but significantly different ($p < .001$) from the DMSO, BaP, and curcumin plus BaP groups. The PE levels in DMSO and curcumin plus BaP groups were similar ($p > .05$). The highest PE level was detected in BaP group, and it was significantly different ($p < .01$) than the other groups. The VF level among the groups was almost similar to the PE mean results. The lowest VF was observed in control and curcumin groups and there was a similarity ($p > .05$) between these two groups. Corn oil group's VF followed these groups, and it was similar ($p = .317$) to both control and curcumin groups. The highest VF level was observed in the BaP group, and it was significantly different ($p < .001$) than the other groups. The statistical difference between groups for GBMF was similar to the VF results. Brief results for the statistical analyses of TEM degradations are shown in Table 1. Mean of degeneration criteria in TEM was presented in Figure 4.

Figure 3. Scanning electron microscopic (SEM) images of kidney glomerulus. Control (**a**), Corn oil (**b**) and DMSO (**c**) groups showing intact glomerular surface structure with secondary foot processes and filtration slits (⋆), podocyte (P), primary (→) and secondary (⇉) foot processes (Inset A: podocyte, secondary foot processes; Inset B: with secondary foot processes and filtration slits). BaP (**d**) group showing prominent distorted shaped podocyte (P), primary (→) foot processes and secondary foot processes and filtration slits (★). Curcumin (**e**) group demonstrating glomerulus with normal appearance. Podocyte cell body, primary and secondary foot processes, secondary foot processes and filtration slits are seen in Curcumin plus BaP (**f**) treated group (Gold-Palladium, scale bars: 2 µm).

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Table 1. Statistical results of TEM degradation analyses. Different superscript among the groups for each column indicates significantly differences between groups.

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Scanning electron microscopic (SEM) results

SEM micrographs of the glomerulus in the control group revealed normal convoluted dispersed capillaries and large cell bodies of podocytes that extend to them, primary and secondary foot processes, and filtration slits (Figure 3A). SEM findings from the groups that received corn oil (Figure 3B) and DMSO (Figure 3C) were similar to those of the control group. The most remarkable changes were observed in the BaP administered group. Podocyte cell bodies and their primary and secondary processes both showed noticeable disruptions. Podocytes and secondary

cavitied podocyte cell bodies (Figure 3D). Podocyte cell bodies were prominent and pedicels were normal and regular in the curcumin group (Figure 3E). The entire structure of the curcumin plus BaP group was similar to that of the control group (Figure 3F).

Figure 4. Graph showing the results of statistical analysis of transmission electron microscope (TEM) degradations. EDPC: electron-dense intramembraneous deposits in podocyte cytoplasm, EDMC: electron-dense deposits in mesengial cell cytoplasm, PE: pedicel effacement, VF: large vacuole formation, GBMF: folding of glomerular basement membrane.



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When SEM degenerations were evaluated statistically, the lowest PE was observed in control, corn oil, and curcumin groups. There were similarities ($p > .05$) among these groups. The PE was significantly higher ($p < .001$) in DMSO and curcumin plus BaP groups compared to the rest of the groups. The highest PE mean was obtained in BaP group and results of this group were significantly different ($p < .001$) than the other groups. The mean PCD level in control, corn oil, and curcumin was the lowest among all of the groups. These groups were significantly lower ($p < .001$) than the DMSO, BaP, and curcumin plus BaP groups. The PCD level in DMSO and curcumin plus BaP groups was significantly different ($p < .001$). The highest PCD level was observed in BaP group and the results of this group were significantly different

SEM degradations are shown in Table 2. Mean of degeneration criteria in SEM was presented in Figure 5.

Figure 5. Graph showing the results of statistical analysis of scanning electron microscope (SEM) degradations. PE: pedicel effacement, PCD: distortion of podocyte cell morphology, PSPD: distortion of primary and secondary podocyte cell processes.



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Table 2. Statistical results of SEM degradation analyses. Different superscript among the groups for each column indicates significantly differences between groups.

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Discussion

This study was designed to investigate the toxic effects of benzo(a)pyrene and the possible protective impacts of curcumin as a promising antioxidant on rat kidney

effects by using transmission and scanning electron microscopic methods. According to the results of this study, administration of daily 10 mg/kg dose of BaP for six weeks altered kidney ultrastructure and these findings were compatible with our scanning electron microscopic evaluation. BaP administration also caused changes in proximal tubules and curcumin treatment at a dose of 100 mg/kg ameliorated these alterations through its antioxidant and anti-carcinogenic features.

In studies of the responses of kidney podocyte cells to various damage stimuli, it was observed that podocyte foot processes were deleted and that these processes widened and narrowed the filtration slits and these findings were interpreted as an indicator of the kidney pathology.[24,25] A study that investigated the lithium treatment effects on the filtration barrier ultrastructure has reported vesicular structure formation and autophagosomes in podocytes and a reduction in endothelium fenestrae.[26] Avasthi et al.[27] have focused on the endothelial cell alterations in uranyl nitrate-induced acute renal failure, and marked deterioration was reported in endothelial cell fenestrations. In our previous study,[22] we examined the protective role of resveratrol and the toxic effects of di (n) butyl phthalate (DBP) on the kidney at the ultrastructural level. We observed thickening and folding of the glomerular basement membrane, electron dense bodies in the cytoplasm of all glomerular structures, and effacement of primary and secondary foot processes. Similar to our study design, Eid et al.[28] investigated the ultrastructural changes in amiodarone-induced nephrotoxicity and the effects of antioxidant grape seed extract. Amiodarone has been reported to cause ultrastructural changes, including impaired glomerular capillaries, podocytes, and mesangial cells, but these morphological findings were ameliorated in the group that received a combination of amiodarone and grape seed extract. Tarladacalisir et al.[29] examined the possible protective effect of vitamin C, in cisplatin-induced damage to kidney by transmission electron microscope. Similar to Tarladacalisir et al.[29] and other studies, we used curcumin as an antioxidant and benzo(a)pyrene as a toxic agent in the present study. We observed severe degenerative findings in the glomerular basement

a significant deterioration in endothelial cell fenestra after BaP administration, suggesting that BaP could decrease the ultrafiltration coefficient by reducing the filtration area of the glomerular capillaries.

Chihanga et al. reported the brush border number, length, and structure abnormalities in ischemia-reperfusion injury-related kidney proximal tubular ultrastructural changes.[30] On the other hand, Houghton et al.[31] have focused on proximal convoluted tubules in their study investigating the toxic effect of gentamicin sulfate, and Eid et al.[28] also examined the toxicity of amiodarone in proximal and distal convoluted tubules. El-Gerbed[32] reported deltamethrin-induced swollen mitochondria, irregularly arranged microvilli, increased number of lysosomes and numerous vacuoles in proximal tubule epithelium. Consistent with the proximal convoluted tubule TEM findings of these studies, we detected an increasing number of large irregular, dense lysosomes, enlarged vacuoles, swollen and rounded mitochondria in the cell cytoplasm, distorted apical brush border, and damaged basement membrane in the cells of tubules in BaP treated group.

Scanning electron microscopic examination of the adverse effects of aminonucleoside on kidney tissue has revealed enlarged podocyte cell bodies and effacement in secondary foot processes.[33] Another study reported distortion in podocyte morphology and foot process effacement in high dose DBP-induced nephrotoxicity.[22] Similar to these findings, we detected remarkable cavities that formed on the surface of podocyte cells in the BaP group, resulting in aberrant cell shapes. This irregularity, which is accompanied by foot process effacement, could be correlated with the intracytoplasmic degenerative changes or caused by collapsed BaP crystals.

Curcumin has been utilized for centuries as a traditional therapeutic agent in a variety of diseases, including liver and biliary diseases and rheumatism, due to its antioxidant and diverse biological activities.[13,14] 2–4 teaspoons of powder containing 200 mg/kg per day have a therapeutic effect. Curcumin has long been used as a

methotrexate-induced nephrotoxicity were reported.[18] Curcumin has been shown to ameliorate gentamicin-induced oxidative damage in kidney by lowering lipid peroxidation damage and increasing antioxidant levels.[35] In chronically administered cyclosporine-related oxidative stress and acute renal failure, Tirkey et al.[36] observed degenerative histological alterations such as glomerular basement membrane thickness. It was reported that the tissue restored to its normal morphology with the curcumin administration, but a small amount of edema has persisted in the tubule cells. Venkatesan et al.[37] have found that curcumin improved kidney function in adriamycin-induced nephrotoxicity by increasing glomerular filtration rate, reducing oxidative stress, and increasing glutathione peroxidase power. Garg et al.[38] examined the effects of curcumin on BaP-induced phase I and phase II enzyme regulation. BaP was dissolved in corn oil and 1 mg/kg dose was orally administered to adult male mice. It was reported that BaP-stimulated DNA particle production, oxidative damage, and inflammation decreased as a result of a reduction in phase I and phase II enzyme stimulation with curcumin administration.[39] In a study investigating the suppressive role of dietary consumed curcumin in benzo(a)pyrene-stimulated gastric cancer, it was reported that curcumin may inhibit gastric tumor formation by acting on all activation pathways and pathways that deactivate BaP metabolism in the liver.[39] Recent studies investigating the histopathological effects of BaP and the role of curcumin in the lung, liver, kidney, and stomach, have revealed curcumin has the potential to inhibit gastrointestinal tumorigenesis and lung injury.[33,40] Similar to previous studies we designed coadministration of curcumin and BaP in order to observe their combined effects on kidney tissue. According to the findings of the present study, curcumin ameliorated the BaP-induced nephrotoxic effects in glomeruli and proximal convoluted tubules. The statistical comparison of all these data was significant ($p<0.05$).

In conclusion, our transmission and scanning electron microscope results showed that BaP is a nephrotoxic agent based on all of the abnormalities following its

curcumin in benzo (a) pyrene-induced neprotoxicity. Moreover, further studies are required to examine the possible effects of curcumin in several organs by using various parameters and microscopic techniques.

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Disclosure statement

No potential conflict of interest was reported by the authors.

Ethics committee approval

This study was conducted at Gazi University, Medical School Experimental Animal Breeding and Experimental Research Center and were approved by Gazi University Local Ethics Committee for Animal Experiments (Approval No. G.U.ET-12.011).

Authorship contributions

Concept: DŞA, DE, GTK, GEG, ÇE; Design: DŞA, DE, GTK, GEG, ÇE; Data acquisition and analysis: DŞA, DE, GTK, GEG, UŞ, ÇE; Critical revision of the manuscript: DŞA,

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