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The exposure to formaldehyde causes renal dysfunction, inflammation and redox imbalance in rats

Camila de Oliveira Ramos[a], Clarissa Rodrigues Nardeli[a], Keila Karine Duarte Campos[a], Karina Braga Pena[a], Dafne Fernandes Machado[a], Ana Carla Balthar Bandeira[b], Guilherme de Paula Costa[c], André Talvani[c], Frank Silva Bezerra[a,*]

[a] Laboratory of Experimental Pathophysiology (LAFEx), Department of Biological Sciences (DECBI), Center of Research in Biological Sciences (NUPEB), Federal University of Ouro Preto (UFOP), Ouro Preto, MG, Brazil
[b] Laboratory of Metabolic Biochemistry (LBM), Department of Biological Sciences (DECBI), Center of Research in Biological Sciences (NUPEB), Federal University of Ouro Preto (UFOP), Ouro Preto, MG, Brazil
[c] Laboratory of Immunobiology of Inflammation (LABIIN), Department of Biological Sciences (DECBI), Center of Research in Biological Sciences (NUPEB), Federal University of Ouro Preto (UFOP), Ouro Preto, MG, Brazil

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ABSTRACT

Twenty-eight Fischer male rats were divided into four groups: control group (CG), exposed to the ambient air, and groups exposed to formaldehyde (FA) at concentrations of 1% (FA1%), 5% (FA5%) and 10% (FA10%). Kidney function was assessed by dosage of uric acid, creatinine and urea. Morphometry was performed on the thickness of the lumen of Bowman's capsule and diameter of the lumen of the renal tubules. We evaluated the redox imbalance through the catalase and superoxide dismutase activity as well as oxidative damage by lipid peroxidation. Inflammatory chemokines CCL2, CCL3 and CCL5 were analyzed by enzyme immunoassays. There was an increase in the concentration of urea in FA10% compared with CG and FA1%. The levels of creatinine, renal lumen and lipid peroxidation increased in all FA-treated groups compared with CG. The concentration of uric acid in FA10% was lower compared with all other groups. There was an increase in the space of Bowman's capsule in FA5% and FA10% compared with CG and FA1%. However, the superoxide dismutase activity was higher in FA5% compared with other groups while CCL5 was higher in FA1% compared with CG. The exposure to formaldehyde in a short period of time leads to changes in the kidney function, inflammation and morphology, as well as promoted the increase of superoxide dismutase activity and oxidative damage.

1. Introduction

Formaldehyde (FA) is a colorless gas, highly soluble in water and irritates in its pure form. FA is a contaminating compound commonly found in the environment due to its wide use in industries such as the production of building materials, textiles, sterilization of products, plastics and cosmetics (Bakar et al., 2015; Checkoway et al., 2015; Ciftci et al., 2015). FA can also be found in cigarette smoke, in car emissions, fuel oil and natural gas, contributing to increased air pollution (Zararsiz et al., 2007b). The exposure to FA is increasingly common, either by environmental or laboratory conditions, where professionals and/or students in the medical field are constantly exposed (Schroeter et al., 2014; Zararsiz et al., 2007b). FA is also endogenously produced by the L-methionine metabolism, histamine, methanol and methyl alanine, being a key intermediate for the biosynthesis of purines and other amino acids (Checkoway et al., 2015; Gulec et al., 2006).

In 2006, the International Agency for Research on Cancer (IARC) described FA as a carcinogen (IARC, 2006). In addition, several studies have shown that chronic exposure to FA may also result in sensory irritation, salivation, dyspnea, headache, insomnia, seizures and neurodegenerative disorders (Bakar et al., 2015; Gulec et al., 2006). The toxicity caused by the exposure to FA by aerobic metabolism and by inflammation can lead to the production and the release of reactive oxygen species (ROS) (Birben et al., 2012; Gulec et al., 2006; Saito et al., 2005). At low concentrations, ROS have physiological functions in cellular processes, but in high amounts, they can cause adverse changes in the cell components, including proteins, lipids and deoxyribonucleic acid (DNA) (Birben

* Corresponding author.
E-mail address: franksbezerra@hotmail.com (F.S. Bezerra).

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et al., 2012; Saito et al., 2005). A change in the balance between oxidant/antioxidant in favor of oxidants is named oxidative stress (Birben et al., 2012). To protect against the deleterious effects of ROS, the cells present a complex enzymatic antioxidant defense system including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) (Gulec et al., 2006; Matsuoka et al., 2010).

Studies have shown that prolonged exposure to FA can result in degeneration and necrosis of proximal tubule kidney and consequently impaired urinary system (IARC, 2006; Kum et al., 2007; Zararsiz et al., 2007b). Furthermore, the exposure to FA induces a number of pathophysiological conditions, including inflammatory diseases by interfering in the concentration of T $CD3^+$ cells, natural killer (NK) cells, TNF, IL-6 and IL1–β (Lino-dos-Santos-Franco et al., 2011; Moro et al., 2016; Seow et al., 2015). The kidney is one of the most sensitive organs to the inflammation and is an important source of chemokines and cytokines in the tubular epithelium due its close contact with high blood flow (Grunz-Borgmann et al., 2015). Thus, the aim of the study was to analyze the oxidative effects on renal inflammatory response in Fischer rats exposed to different concentrations of FA.

2. Materials and methods

2.1. Animals

Twenty-eight male Fischer rats, between 10 and 12 weeks of age and body mass 180–200 g from the Experimental Nutrition Laboratory of the Federal University of Ouro Preto, were used in this study. The animals were kept in boxes with environment temperature, controlled light and humidity (21 ± 2 °C, 12-h cycles of light/dark, 50 ± 10%, respectively) receiving commercial diet for rat and water, both *ad libitum*. This study was performed in accordance with standards of animal protection and the ethical principles of the Brazilian Society of Science in Laboratory Animals and approved by the Ethics Committee on Animal Use of this university (Protocol 2011/01).

2.2. Exposure to formaldehyde (FA)

Animals were exposed to FA by an ultrasonic nebulizer (Unique Group, Indaiatuba, São Paulo, Brazil) coupled to an inhalation chamber of 30 L (25 cm × 30 cm × 40 cm). Three groups of 7 animals were exposed to different concentrations of FA (1% 5% and 10%) and a control group exposed to ambient air. The exposure proceeded for 20 min, 3 times a day (morning, afternoon, evening) for 5 consecutive days (Maiellaro et al., 2014; Murta et al., 2016). After 24 h of the experimental protocol, the animals were euthanatized with an overdose of Ketamine (50–75 mg/kg) and Xylazine (5–10 mg/kg) intraperitoneally.

2.3. Homogenized tissue

After euthanasia, the right kidney was removed and homogenized in 1 mL of pH 7.5 potassium phosphate buffer and centrifuged at 10.000 × *g* for 10 min at 4 °C. The supernatant was collected and stored in a freezer at −80 °C for biochemical analyses.

2.4. Renal function

Blood was obtained by cardiac puncture and collected into tubes. After, the samples were centrifuged at 10.000 rpm for 10 min. Serum was collected for analyses of uric acid, creatinine and urea. Analyses were spectrophotometrically performed using commercial kits (Bioclin®, Belo Horizonte, Brazil).

2.5. Histology and morphometric analyses

The left kidney was removed and immersed in fixative solution containing 4% formaldehyde for 48 h. Serial sections were performed to four micrometers thick, which were stain with hematoxylin-eosin (HE) for histopathological analyses. The variables analyzed were: Bowman's space and the lumen of the renal tubules. Bowman's space was calculated by the area of the Bowman's capsule and the glomerular tuft and subtracted from the second of the first area. Glomeruli were evaluated in the afferent artery measuring hence the equatorial portion of the glomerulus. The lumen of the renal tubules was calculated by tracing the boundaries thereof by ImageJ® software (National Institutes of Health, Bethesda, Maryland, USA)

2.6. The activity of catalase (CAT)

CAT activity was measured as the decreased rate of hydrogen peroxide to an absorbance of 240 nm represented by U/mg of the protein (Aebi, 1984). Protein content was performed on samples of tissue homogenate by the method of Bradford (Bradford, 1976).

2.7. The activity of superoxide dismutase (SOD)

SOD activity was measured in the tissue according to the Marklund method (Marklund and Marklund, 1974) which is based on the enzyme's ability to inhibit the autoxidation of pyrogallol. The absorbance was read in the ELISA reader at 570 nm. Protein content was performed on samples of the homogenate tissue by the method of Bradford (Bradford, 1976).

2.8. Analysis of oxidative damage

Lipid peroxidation was determined by testing reactive substances thiobarbituric acid (TBARS) described by Buege (Buege and Aust, 1978). The homogenized tissue was centrifuged for 10 min at 13.000 rpm and the supernatant was read in a spectrophotometer at 535 nm. The concentration was represented in nmols per milligram of the protein (nmol/mg protein).

2.9. Immunoassays

The renal parenchyma was used for the evaluation of the inflammatory chemokines CCL2, CCL3 and CCL5. The immunoassays were performed in 96-well plates by the addition of the 100 μL of a monoclonal antibody to protein (or peptide) of interest, diluted in PBS containing 0.1% bovine serum albumin-BSA (SIGMA). After 12 h at room temperature incubation, the plates were blocked with 300 μL/well of a PBS/1% BSA solution for 1 h at 37 °C. Samples were applied in a volume of 100 μL to each well. The avidin-HRP (1:2000) and the substrate ABTS liquid were used at the end of the reaction before the reading an ELISA reader at 490 nm. All chemokine ELISA kits were purchased from Peprotech (Ribeirão Preto, Brazil) and performed according to the manufacturer recommendations.

2.10. Statistical analysis

The normal distribution of each variable was assessed using the Kolmogorov-Sminorv test and presented as mean ± standard error of mean (SEM). For comparison among groups, a one-way ANOVA followed by Tukey's post-test was used. We used the Kruskal-Wallis test followed by Dunn's post-test for discrete data and expressed them as median, minimum and maximum values. In both cases, the difference was considered significant when p value was <0.05. The statistical analyses were performed using

GraphPad software (GraphPad InStat version 5.00 for Windows 7, GraphPad Software, San Diego, CA USA).

3. Results

3.1. Renal function

Renal function was assessed through the analysis of urea concentration (mg/dL), creatinine (mg/dL) and uric acid (mg/dL) in serum (Fig. 1). There was an increase of urea concentrations in FA10% compared with CG and FA1% ($p = 0.001$) (Fig. 1A). The creatinine levels increased in all treated groups compared with CG ($p = 0.003$) (Fig. 1B). However, the concentration of uric acid in FA10% was lower compared with the other groups ($p < 0.0001$) (Fig. 1C).

3.2. Morphometry

In this study, there was an increase in Bowman's space in FA5% and FA10% compared with CG and FA1% ($p < 0.0001$) (Fig. 2A). The lumen of the renal tubules was elevated in all groups exposed to formaldehyde compared with CG ($p < 0.0001$) (Fig. 2B). Fig. 3 shows the increase in Bowman's space FA10% and thickness increase in the lumen of the renal tubules the renal tubule FA1%.

3.3. Redox imbalance

The redox imbalance was assessed through the measurement of the activity of antioxidant enzymes SOD and CAT. The SOD activity increased in FA5% compared with the other groups ($p = 0.0083$). The CAT activity did not change significantly among the groups of animals exposed to formaldehyde ($p = 0.714$). Lipid peroxidation was measured through the formation of thiobarbituric reactive substances (TBARS) in renal homogenized tissue to check the possible oxidative damage caused by different formaldehyde concentrations in the kidneys. There was an increase of TBARS in all treated groups compared with CG ($p < 0.0001$). Furthermore, the lipid peroxidation was significantly higher in FA10% compared with FA1 ($p < 0.0001$) (Table 1).

3.4. Kidney chemokine measurement

The chemokines CCL2, CCL3 and CCL5 were measured through enzyme immunoassays in renal tissue homogenate. High levels of CCL2 were observed in FA1% and FA5% compared with CG ($p = 0.0044$). High levels of CCL3 were also observed in FA1% and FA5% compared with CG. On the other hand, the levels of CCL3 was lower in FA10% compared with GC, FA1% and FA5% ($p < 0.0001$). Finally, the kidney levels of CCL5 chemokine was higher in FA1% compared with CG, FA5%, and FA10% ($p < 0.0001$) (Table 2).

4. Discussion

In this study, we analyzed renal function, oxidative effects and inflammatory response in rats exposed to different concentrations of formaldehyde for 5 consecutive days. Clinical and experimental studies have shown the toxic effects of FA in the urinary system (Zararsiz et al., 2007b, 2006). In our present study an increase in

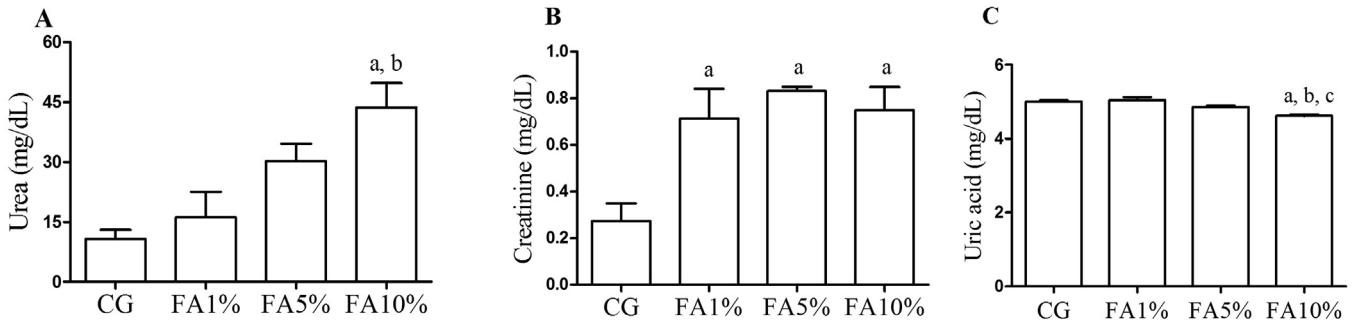

Fig. 1. Effects of the exposure to FA in levels of biomarkers the kidney function. The letter (a) represents a significant difference compared to CG. Letters (b,c) represents a significant differences compared to FA1% and FA5%. Data were expressed as mean ± SEM and were analyzed by one-way ANOVA followed Tukey's post test ($p < 0,05$).

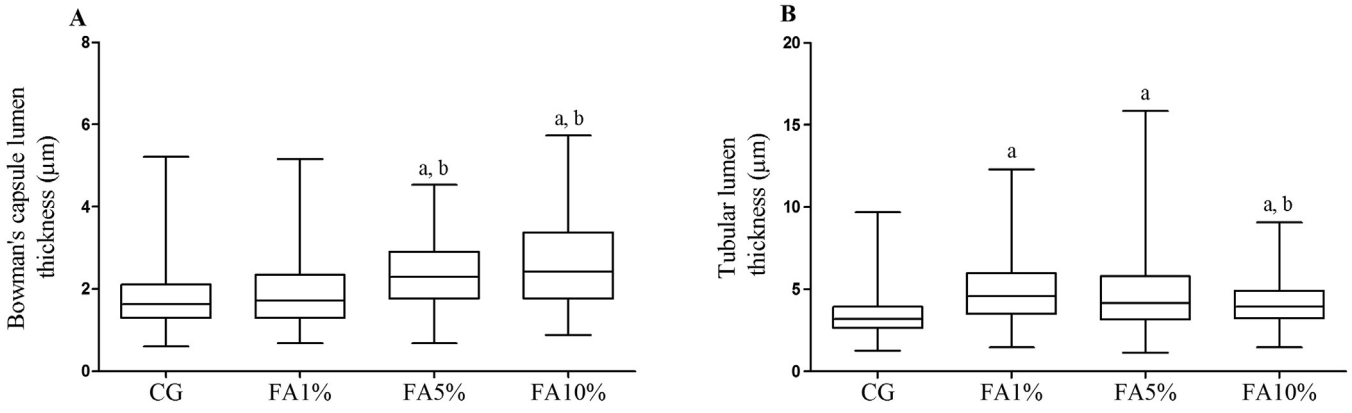

Fig. 2. Morphometric analyses in renal tissue of rats exposed to different concentrations of formaldehyde. (A) Analysis of Bowman's space of rats exposed to different concentrations of formaldehyde. (B) Analysis of lumen of the renal tubules of renal tissue of rats exposed to different concentrations of formaldehyde. The letter (a) represents a significant difference compared to CG. The letter (b) represents a significant difference compared to FA1%. Data were expressed as median, minimum and maximum values and were analyzed by Kruskal- Wallis test followed by Dunn's post test. ($p < 0,05$).

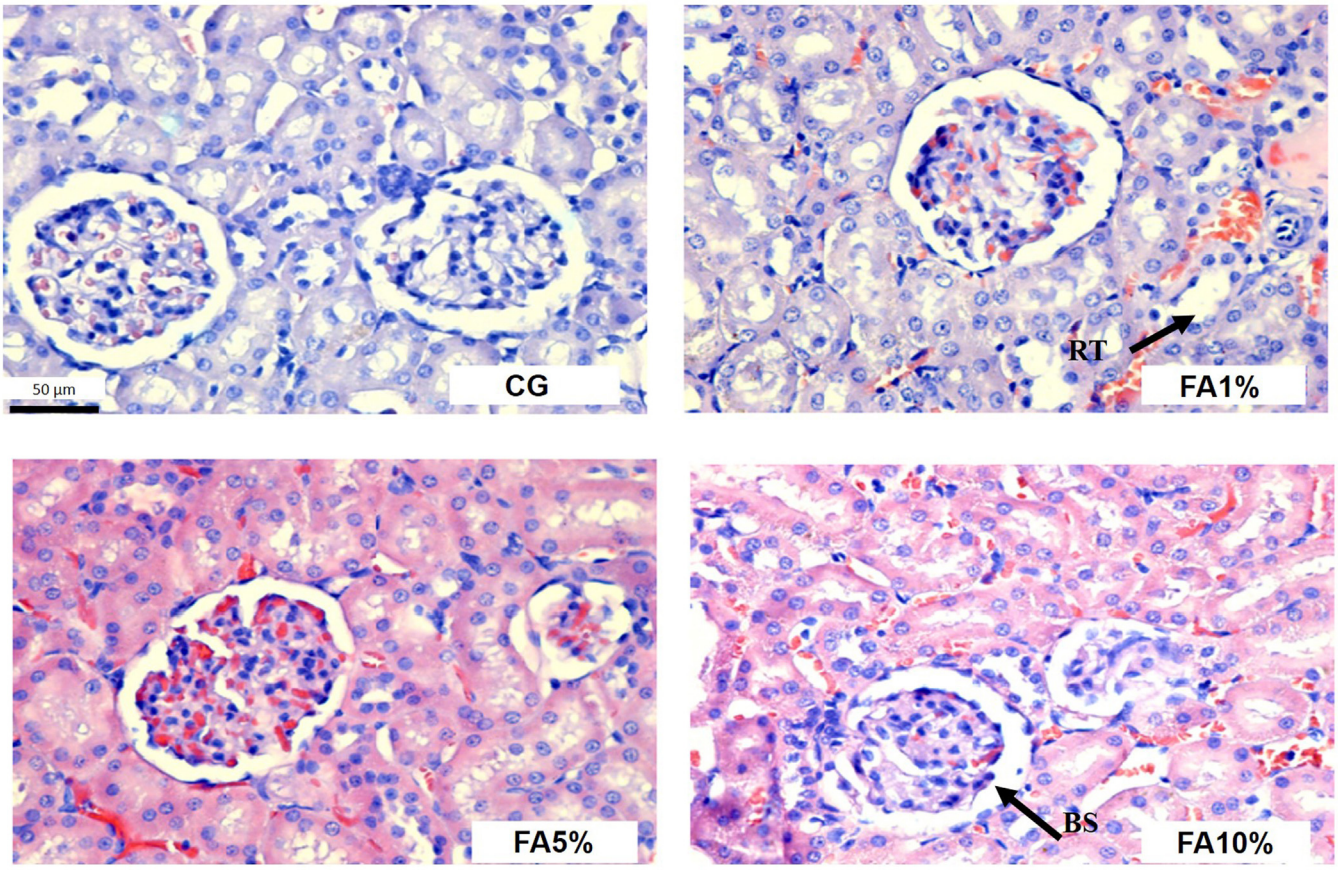

Fig. 3. Photomicrographs of kidney sections stained with hematoxylin and eosin. Barr = 50 µm. Analysis of Bowman's space and the lumen of the renal tubules of renal tissue of rats exposed to different concentrations of formaldehyde. RT shows increased lumen of the renal tubule in FA1% and BS shows increased Bowman's space in FA10% compared to CG.

the Bowman's space and in the lumen of the renal tubules of the exposed group was observed which corroborates with Zararsiz and colleagues' study. These authors examined the toxicity of FA in the kidneys and the protective effects of Ω −3 essential fatty acids against these toxic effects in Wistar rats during 14 days and observed a glomerular and tubular degeneration as well as a remarkable expansion in the distal tubules indicating renal tissue injury in those FA exposed animals (Zararsiz et al., 2006). In this way, another study demonstrating the protective effects of the melatonin on renal damage reinforced the presence of glomerular degeneration, vacuole formation, vascular dilation and congestion in those rats exposure to FA for 14 days, every other day (Zararsiz et al., 2007a). Bakar and colleagues also studied the protective effects of the proanthocyanidin and the vitamin E in the renal damage induced by the exposure to FA in rats and reported epithelial damage of the glomerulus and the membrane of the renal tubules, hypertrophic cells in the tubules and pyknotic nuclei in cells of the loop of Henle (Bakar et al., 2015). Together, these findings show that the exposure to FA leads to the different levels of lesion in the renal tissue which, therefore, would result in releasing of the vasopressor agents, decreasing the vasodilatation and increasing ROS and oxidative stress levels (Bakar et al., 2015; Kunak et al., 2015; Zararsiz et al., 2006).

In our study we observed an increase in serum urea and creatinine in animals exposed to higher concentration of FA compared with the non-exposed group. The relationship between urea and creatinine can be, in particular, useful when there are sharp falls in the glomerular filtration rate. The urea is reabsorbed by the renal tubule after the filtration process which is not applied for the creatinine. A pathological condition (eg. heart failure,

Table 1
Activies of SOD, CAT and TBARS content in kidneys samples from CG, FA1%, FA5% and FA10%.

	CG	FA1%	FA5%	FA10%
SOD (U/mg ptn)	11.76 ± 1.37	13.30 ± 1.07	20.73 ± 3.25[a,b]	13.26 ± 0.84[c]
CAT (U/mg ptn)	3.39 ± 0.23	3.47 ± 0.24	3.09 ± 0.50	3.63 ± 0.30
TBARS (nmol/mg ptn)	0.27 ± 0.01	1.19 ± 0.20[a]	1.83 ± 0.26[a]	1.87 ± 0.06[a,b]

The letters represent significant differences among groups. The letter (a) represents a significant difference compared to CG. The letter (b) represents a significant difference compared to FA1% and the letter (c) represents a significant difference compared to FA5%. Data are expressed as mean ± SEM and were analyzed by one-way ANOVA followed by Tukey's post-test ($p < 0.05$).

Table 2
Level of CCL2, CCL3 and CCL5 of the kidney parenchyma samples from CG, FA1%, FA5% and FA10%.

	CG	FA1%	FA5%	FA10%
CCL2 (pg/mL)	1966 ± 48.12	2274 ± 45.41[a]	2271 ± 62.45[a]	2084 ± 75.61
CCL3 (pg/mL)	388.20 ± 12.51	485 ± 14.17[a]	440 ± 25.16[a]	314 ± 12.88[a,b,c]
CCL5 (pg/mL)	401.70 ± 16.33	788.6 ± 49.55[a]	466 ± 22.79[b]	537.50 ± 55.31[b]

The letters represent significant differences among groups. The letter (a) represents a significant difference compared to CG. The letter (b) represents a significant difference compared to FA1% and the letter (c) represents a significant difference compared to FA5%. Data are expressed as mean ± SEM and were analyzed by one-way ANOVA followed by Tukey's post-test ($p < 0.05$).

dehydration, feverish and chemical toxicity conditions) which stimulates tubular reabsorption of sodium determines an increase in the proportion of urea/creatinine. In addition, oxidation of FA for formic acid is catalyzed by various enzymes such as NAD-dependent dehydrogenase formaldehyde, xanthine oxidase, catalase and peroxidase. Then, the increase of urea may be associated with the high production of these enzymes used for the detoxification of the FA (Kum et al., 2007; Teng et al., 2001). Some studies have suggested that creatinine, the end metabolite of creatine phosphate, besides its antioxidant properties, is an important marker of nephrotoxicity. Increased serum levels of creatinine strongly suggest failure in kidney function due to the exposure to FA (Kunak et al., 2015; Milovanovic et al., 2015).

The uric acid is the end product of the metabolic pathway of purines and is considered a natural antioxidant with chelating properties in the presence of metal intoxication. In addition, uric acid has a scavenger capacity of Reactive Nitrogen Species (RNS) and the superoxide anion, thereby helping to block the formation of the highly reactive peroxynitrite oxidant (Whiteman et al., 2002; Yang et al., 2015).

A reduction in serum levels of the uric acid in the group exposed to a higher concentration of FA was observed in our study, suggesting that the role of uric acid as scavengers in renal tissue due to oxidative damage generated by FA.

The ROS generation occurs during the conventional cellular respiratory process, being potentiated in the presence of exogenous chemical agencies, such as FA (Bakar et al., 2015; Birben et al., 2012; Saito et al., 2005). Indeed, there is a physiological balance between the reactive species and antioxidant defense system in the body, but any change or disturbance in this equilibrium can start an oxidative stress process (Birben et al., 2012; Campos et al., 2013; Matsuoka et al., 2010; Zararsiz et al., 2006). The oxidative stress can be controlled by endogenous and enzymatic mechanisms performed by CAT, SOD and glutathione (GSH) (Matsuoka et al., 2010; Zararsiz et al., 2006). Kum and colleagues did not observe differences to SOD and CAT levels in the animals exposed to xylene and FA (Kum et al., 2007). However, in the study of Zararsiz et al. there was a reduction in SOD activity in groups exposed to FA (Zararsiz et al., 2007b) while CAT activity was observed in another study where the diaphragm muscle and trachea were evaluated in Fischer rats exposed to FA (Lima et al., 2015). Our study showed no significant changes in CAT among all the groups, however, a significant difference in SOD among FA groups was observed. These data suggest that the FA is able to break the antioxidant defense mechanisms in the kidneys and lead to the formation of oxidative stress (Zararsiz et al., 2007b).

FA develops cytotoxic effect by forming a crosslinking between proteins and DNA resulting in damage that could lead to cancer or cell death, and the formation of reactive species can accelerate this process (Saito et al., 2005; Zararsiz et al., 2007b). The increase of TBARS is an indication of oxidative damage to the lipid peroxidation process and thus a marker widely used to demonstrate oxidative stress (Bakar et al., 2015; Lima et al., 2015; Zararsiz et al., 2006). This increase of TBARS can result in changes in the structure and permeability of the cell membrane and consequently stimulate the release of cytotoxic compounds as malondialdehyde (MDA) (Campos et al., 2013; Lima et al., 2015). Our results corroborate previous studies in which an increase in MDA levels in groups of animals exposed to FA was observed, suggesting an association of oxidative damage in kidney tissue caused by the toxicity of FA (Bakar et al., 2015; Ciftci et al., 2015; Lima et al., 2015; Zararsiz et al., 2006).

Finally, the renal damage is usually accompanied by an important and local inflammatory process which promotes the infiltration of cells mainly conducted by chemokines. Chemokines are small chemotactic cytokines activated by inflammatory cells and with the capacity to recognize a variety of leukocytes (Jung et al., 2015; van der Veen et al., 2009). The increase in the levels of chemokines such as CCL2, CCL3 and CCL5 has been associated with the influx of cells such as monocytes, lymphocytes and eosinophils into tissues and fluids (Capelli et al., 2005; Conti and DiGioacchino, 2001). Supported by these concepts, in this study we observed high levels of CCL2, CCL3 and CCL5 in the renal parenchyma of animals exposed to lower FA concentrations. Other studies have previously demonstrated that increased CCL2, CCL3 and CCL5 in the parenchyma were strongly associated with the worsening in the renal inflammatory injury (Anders et al., 2003; Keepers et al., 2007; Nishihara et al., 2013). In conclusion, our results demonstrated that the exposure to formaldehyde in a short period of time leads to changes in the kidney function, inflammation and morphology, as well as promoted the increase of superoxide dismutase activity and oxidative damage.

Conflicts of interest

There are no conflicts of interest.

Acknowledgments

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