Influence of Oral Melatonin Administration on Oxidative Stress and Intestinal Microflora in Rats Exposed to Cadmium

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ABSTRACT

The aim of the present study was to evaluate the effects of oral melatonin treatment on oxidative stress and intestinal microflora in rats exposed to chronic cadmium. Healthy 32 adult male albino Wistar rats were randomly divided into four groups as control (C; n=8), cadmium (Cd; n=8), melatonin (Mlt, n=8), cadmium + melatonin (Cd + Mlt; n=8). Mlt (100 mg/kg) was orally administered 5 times (Mlt and Cd + Mlt), and CdCl₂ (2 mg/g day) 3 times a week for 4 weeks to rats (Cd and Cd + Mlt). After the treatments, serum total antioxidant status (TAS), total oxidant (TOS) levels as well as plasma ALT, AST, GGT, T.pro, Alb and BUN values were measured. Intestinal contents were aseptically collected, and Enterobacteriaceae, Lactococcus spp. and Lactobacillus spp. counts were performed. As a result, serum TOS levels were defined higher in Cd group than other groups (P<0.05). Lactococcus spp. counts decreased as 0.63 log in Cd group compared to C in small intestine, however it increased as 1.15 log in Cd + Mlt group. In conclusion, Cd + Mlt chelate was found beneficial for intestinal microflora due to suppressed the Enterobacteriaceae growth, however ameliorated the Cd induced oxidative stress and Lactobacillus spp./Lactococcus spp. rates in the different part of the intestine.

Keywords: Cadmium, Melatonin, Microflora, Oxidative Stress, Rat

INTRODUCTION

Cadmium (Cd) is, a toxic heavy metal, an important environmental pollutant that widely distributed in agricultural and industrial areas, especially in the atmosphere (Cook et al. 1994). It has been used in industrial area as an anti-corrosive agent for steel, iron and other composites. The main source of exposure to the toxic and carcinogenic (as a group I carcinogen) this metal are heating Cd-containing materials such as smelting and electroplating, using of paint pigments and cadmium-nickel batteries, and also living close to extensive industrial areas. Generally, human are mostly exposed to Cd through the intake of contaminated water, food (especially vegetables) or air as well as inhalation of tobacco smoke (Goyer et al. 1986; WHO 1993; ATSDR 1999).
Although long-term exposure to Cd causes many toxic effects in various organ and systems such as brain, lung, bones, immune, haemopoietic, endocrine, cardiovascular and reproductive in human and animals, it mainly accumulates in the kidney/liver tissues and impairs their functions. These disturbances lead to elevation of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and blood urea nitrogen (BUN) levels which are indicator markers of the tissue damage in the blood. It is also affected the plasma protein synthesis and rates. Besides, Cd is known to cause oxidative stress by increasing lipid peroxidation and/or by changing intracellular antioxidant/oxidant rates (Figueiredo-Pereira et al. 1998; Fowler 2009; Satarug et al. 2010). The gastrointestinal (GI) tract is susceptible to the attacks of foreign harmful substances which orally ingested. In the normal microflora of GI tract, there is an important relationship between the bacteria population and the intestinal epithelial cells which is known as symbiosis. It play a critical role for health of the organism due to improving the microbial balance, detoxification and elimination of harmful compounds such as heavy metals from the system by removing through precipitation. The presence of commensal bacteria in the intestinal tract also provides the first barrier of defense against pathogenic bacteria. Imbalance in the relationship among the intestinal epithelial cells, pathogen and/or commensal bacteria population causes GI disorders (Tancrede 1992; Bengmark 1997; Hooper et al. 2001; Eckburg et al. 2005). Heavy metals such as mercury (Hg), cadmium (Cd), arsenic (As), chromium (Cr), thallium (Tl), lead (Pb) and pathogenes reach GI tract through ingestion of contaminated food and water (Upreti et al. 2004; Inaba et al. 2005; Monachese et al. 2012). However, the toxicological effect of heavy metals, especially Cd, on GI microflora, is still remains unclear.

In recent years, it has been enounced that the harmful effects of Cd can be ameliorated by using some substances which have antioxidant and metal binding properties. Many chelating agents, antioxidants and vitamins have been used to lessen oxidative stress and also tissue damage due to Cd (Fournorad et al. 2006; Fang 2007; Karabuht-Bulan et al. 2008; El-Bozhy et al. 2014). One of them is Mlt (N-acetyl-5-methoxytryptamine) is a hormone secreted from the pineal gland, accepted as a powerful antioxidant and free radical consumer substance due to its lipophilic properties. In addition, it has metal binding properties, and regulatory effect on the intestinal microflora which was also determined, recently (Reiter et al. 2000; Karbownik et al. 2001; Zhu et al. 2018).

Therefore, the present study has been designed to evaluate the effects of oral Mlt treatment on oxidative stress and intestinal microflora in rats exposed to chronic cadmium toxicity.

MATERIALS and METHODS

Animals

In study, healthy 32 adult male albino Wistar rats (body weight ~ 200 ± 30g) were used. During the experiment, rats were housed in standard plastic rat cages (at 23±2°C room temperature, 55 ± 10% relative humidity, 12 hours night/day light period) and fed ad libitum standard rat feed. The animals also had fresh drinking water during the experiment. All experimental procedures were approved by the Ethical Committee on Animal Experimentation of the University of Balıkesir (Turkey, project code number 2019/4-6).

Study Design and Experimental Procedure

After acclimatization, animals were randomly divided into four groups as control (C; n=8), cadmium (Cd; n=8), melatonin (Mlt; n=8), cadmium + melatonin (Cd + Mlt; n=8), and following applications were performed:

- **Control Group (C):** Standard rat feed and fresh drinking water were given to rats ad libitum throughout the experiment.
- **Cadmium Group (Cd):** Cadmium chloride (CdCl₂) (2 mg/day) were orally administered to rats 3 times a week for 4 weeks.
- **Melatonin Group (Mlt):** Melatonin (100 mg/kg) was orally administered to rats 5 times a week for 4 weeks.
- **Cadmium + Melatonin (Cd+Mlt):** Melatonin (100 mg/kg) was orally administered 5 times a week, and cadmium chloride (2 mg/day) was administered 3 times a week for 4 weeks.

At the end of the experiment (4 weeks later), the rats were anesthetized by intraperitoneal injection of ketamine/xylazine (0.1 ml/ 100 mg/body weight) and sacrificed by cervical dislocation technique. Cardiac blood samples were taken via cardiac puncture under the general anesthesia, and collected into heparinized and normal tubes. Plasma and serum samples were separated from the blood samples using a centrifuge (3000 rpm, 25 min, Heilrich, Germany). Obtained plasma and serum samples were stored at minus 80°C in a refrigerator until analysis time.

Determination of total antioxidant and oxidants levels

Serum total antioxidant status (TAS) and oxidant status (TOS) levels were measured by ELISA (Thermoscientific Elisa Reader, USA) using commercial kits (Rel Assay Diagnostics, Gaziantep, Turkey), according to Erel’s method which is automated and colorimetric (Erel 2004, 2005).

Determination of some plasma enzyme levels

Plasma alanine amino transferase (ALT), aspartate amino transferase (AST), gamma glutamyl transferase (GGT), total protein (T.pro), albumine (Alb) and blood urea nitrogen (BUN) values were measured by using biochemical analyser (Architect C-8000, Abbott, USA) with commercial kits according to prospectus of manufacturer.

Microbiological analysis

During the necropsy, 1 g intestinal fluid content were aseptically collected from the small and large intestines of the each rats (separately with 3 replicates). Then, they were homogenized in the stomacher for 2 minutes with sterile 9 ml Maximum Recovery Diluent (MRD), serial dilutions were prepared from 10⁻¹ to 10⁻⁶. For determine to the Enterobacteriaceae count, 1 ml of the dilution was taken and cultured in VRB (Oxoid CM1082) Agar according to the double-plate technique. The plates were evaluated as Enterobacteriaceae because of the observing purple-pink colonies after aerobic incubation at 37°C for 24 hours (Osman et al. 2006). On the other hand, 0.1 ml of the dilution was taken and cultured in the M17 (Oxoid CM0785) agar according to spread plate technique for despite to Lactococcus spp. count. Then, plates were evaluated as Lactococcus spp. depends on occurring yellow-cream colonies after anaerobic incubation at 30°C for 24 hours (Lee et al. 2010). For detection of Lactobacillus spp. count, 0.1 ml of dilution was cultured on MRS (CM0361) agar. Plates were also evaluated as Lactobacillus spp. due
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Statistical differences among the groups were tested by analysis of variance (ANOVA) which is followed by Duncan’s test using SPSS for Windows version 25.0.

RESULTS

Serum TOS levels were defined higher in Cd group than other experimental groups \((P<0.05)\). Mlt treatment alone positive affected the TAS levels in Mlt group animals when compared to other experimental groups \((P<0.05)\), shown in Table 1. Plasma ALT, AST, GGT and BUN enzyme levels were detected higher in Cd group when compared to other experimental groups \((P<0.05)\), shown in Table 2. Above-mentioned enzyme levels decreased due to Mlt administration in Mlt and Cd + Mlt group animals \((P<0.05)\). Administration of Mlt didn’t lead to significant change in the T. pro and Alb values in present study. In the small and large intestines of the control group rats, Enterobacteriaceae, Lactococcus spp. and Lactobacillus spp. counts were detected as 4.34, 4.25 log cfu / g; 6.47, 7.09 log cfu / g and 8.37, 8.63 log cfu / g, respectively. Although the count of Enterobacteriaceae was defined similar in C, Mlt and Cd groups, a significant decrease was found in the Cd + Mlt group in the small intestine \((P<0.01)\). In terms of the count of Enterobacteriaceae in the large intestine, there was not any significant difference among the C, Mlt and Cd + Mlt, it was found a significant difference in Cd group animals \((P<0.01)\). Although there was not a significant difference between the C and Cd groups in terms of Lactococcus spp. count in the small intestine, there was a significant difference between the C and the other experimental groups in the large intestine of the rats. On the other hand, Lactococcus spp. count was found similar in C and Cd groups in the large intestine of the rats, there was a significant difference between the Mlt/Cd + Mlt and C groups \((P<0.01)\). There was a significant difference between the C and the other experimental groups according to Lactobacillus spp. count in the small intestine of the rats \((P<0.01)\). When the large intestines were evaluated, it was found that there was a significant difference between the C group and Cd + Mlt group according to Lactobacillus spp. count \((P<0.01)\).

Table 1. Serum TAS and TOS values of the rats in different experimental groups

| Parameters | C \((n=8)\) | Mlt \((n=8)\) | Cd \((n=8)\) | Cd + Mlt \((n=8)\) |
|------------|-------------|-------------|-------------|-----------------|
| TOS \((\mu\text{mol H}_2\text{O}_2 \text{Eq/L})\) | 23.852±6.860\(^a\) | 17.172±1.996\(^b\) | 39.473±7.380\(^a\) | 37.042±4.832\(^ab\) |
| TAS \((\text{mmol Trolox Eq/L})\) | 1.743±0.016\(^b\) | 1.791±0.015\(^a\) | 1.027±0.007\(^d\) | 1.698±0.177\(^c\) |

\(^a,b,c\); The differences between average values indicated by different letters in the same row of the same parameters are important \((p<0.05)\).

Table 2. The average plasma ALT, AST, GGT, total protein, albumine and BUN levels in experimental groups \((X \pm \text{SEM})\)

| Parameters | C \((n=8)\) | Mlt \((n=8)\) | Cd \((n=8)\) | Cd + Mlt \((n=8)\) |
|------------|-------------|-------------|-------------|-----------------|
| T.Protein \((\text{g/dL})\) | 5.58±0.14\(^a\) | 5.21±0.14\(^a\) | 4.57±0.16\(^b\) | 5.13±0.10\(^a\) |
| ALT \((\text{U/L})\) | 37.83±1.95\(^c\) | 37.66±1.20\(^c\) | 81.00±5.17\(^a\) | 72.82±4.74\(^b\) |
| AST \((\text{U/L})\) | 60.16±4.03\(^c\) | 62.16±5.17\(^c\) | 147.0±16.82\(^a\) | 107.16±9.88\(^b\) |
| GGT \((\text{U/L})\) | 1.16±0.11\(^c\) | 1.15±0.12\(^c\) | 2.50±0.23\(^a\) | 1.40±0.24\(^b\) |
| Albumine \((\text{g/dL})\) | 3.50±0.10\(^a\) | 3.52±0.14\(^a\) | 2.85±0.22\(^b\) | 3.54±0.91\(^a\) |
| BUN \((\text{mg/dl})\) | 18.71±1.22\(^c\) | 16.10±1.34\(^d\) | 40.72±2.26\(^a\) | 30.27±2.25\(^b\) |

\(^a,b,c,d\); The differences between average values indicated by different letters in the same row of the same parameters are important \((p<0.05)\).
DISCUSSION

Although there are many studies about the toxicological effect of heavy metals, especially Cd, on different tissues (liver, kidney and brain) in human and animal body, influences of Cd on GI microflora and its relationship with oxidative stress is still unclear depend on the limited investigations (Gerhardsen et al. 2002; Satarug et al. 2003; Kocak and Akcil 2006; Karabulut-Bulan et al. 2008).

In our study, serum Tos levels were defined higher in Cd group than other experimental groups. Similarly, Cd induced increased blood Tos levels were also detected by Andjelkovic et al. (2019) in a previous study. In addition, exposure the Cd reduced TAS and GSH levels, however increased LPO, H2O2, Tos, OSI values in sublingual gland and kidney tissue samples which were reported by Kumas et al. (2016) and Kostedka-Sochoń et al. (2018). Influence of acute and chronic Cd toxicity on another important antioxidant/oxidant system parameters such as sod, GSH and catalase were also defined by other researchers which was similar with our results, previously (Renugadevi et al. 2010; Bu et al. 2013; Kanter et al. 2013). On the other hand, Mlt (which is a known antioxidant and free radical scavenger) treatment alone positively affected the antioxidant capacity (TAS) in Mlt group animals when compared to Cd + Mlt and Cd groups in present study. It has been reported that treatment of Mlt to chronically Cd exposed male Sprague-Dawley rats for 3 months also decreased the MDA levels, but increased sod, CAT and GSH-Px activities in a previous study (Kaplan et al. 2008). Positive effects of Mlt treatment on Cd induced oxidative damage also confirmed by other researchers (Eybl et al. 2006; El-Sokkary et al. 2009; Shagirtha et al. 2011). It can be considered that the treatment of Mlt ameliorated the Cd induced oxidative stress in present study.

In our study, an important indicators of liver and kidney functions are plasma-alt, ast, GGT and BUN enzyme levels were detected higher in Cd group when compared to other experimental groups which were corresponding with previous studies (Renugadevi et al. 2009; Lakshmi et al. 2012; Kisadere et al. 2019). On the other hand, above-mentioned enzyme levels decreased due to Mlt administration in Mlt and Cd + Mlt group animals in present study. These results were consistent with Alabbsini et al. (2008) and Hussein et al. (2014). Besides, Tpro and Alb levels were found the lowest in Cd group in this study. It was corresponding with Zohouri and Tekeli (1999), Hussein et al. (2009) and Oyinloye et al. (2016). Increased liver and kidney enzyme levels, and reduction of Tpro and Alb values confirm the tissue damage due to chronic Cd accumulation and toxicity in present study. Administration of Mlt didn’t lead to significant change on the Tpro and Alb values, however increased the BUN, ALT, AST and GGT levels in Cd + Mel groups when compared the other groups. It can be explained that Mlt may be partially tolerated the Cd accumulation and toxicity in the liver.

In the small intestinal microflora of the rats, neither Cd nor Mlt didn’t cause any significant changes in the counts of Enterobacteriaceae in present study. On the other hand, Escherichia coli and Klebsiella spp., which are the members of Enterobacteriaceae group, counts were detected sharply decreased due to exposed the different high doses of Cd for 45 days in the small intestine of the mouse by Fazeli et al. (2011). Interestingly, Enterobacteriaceae count was detected the lowest in Cd + Mlt group when compared to other experimental groups (C, Cd and Mlt) in small intestines in our study. The reductional effect of Cd + Mlt on Enterobacteriaceae counts can be explained by either direct antimicrobial effect of chelate or by decreasing the absorption/absorption rate of Cd, and tissue oxidative stress with prolonging the residence time of Cd in the small intestine. In present study, elevated serum antioxidant and decreased oxidant levels can be also confirmed this findings (Cheweatiuk et al. 2006). Besides, Cd treatment led to increase Enterobacteriaceae count in large intestine in Cd group animals when compared to C group. It has been reported that Escherichia coli and Klebsiella spp. counts decreased in the large intestine of the mice due to Cd administration in a previous study which was in consistent with our study (Fazeli et al. 2011). Although it has been suggested that Mlt regulates the all intestinal microbial flora and thus improving intestinal health in previous studies, it was not observed a significant change in Enterobacteriaceae counts in large intestine of the Mlt/Cd + Mlt group animals (Zhu et al. 2018). These differences can be occured due to different dose, time of exposure to Cd and/or animal species. In addition, the count of Enterobacteriaceae in the Cd + Mlt group was similar with the C group in our study. It is indicated that the chelate stabilizes the Cd-induced tissue/serum oxidative stress, and the increase of Enterobacteriaceae count in the Cd group is thought to be due to the lack of Cd absorption from the large intestines, therefore the

Table 3. The average counts of Enterobacteriaceae, Lactococcus spp. and Lactobacillus spp. in different parts of the rat intestine

| Groups                  | Intestine | Enterobacteriaceae | Lactococcus spp. | Lactobacillus spp. |
|-------------------------|-----------|--------------------|------------------|--------------------|
| Control (n:8)           | Small     | 4.34±0.08abc       | 6.47±0.00bc      | 8.37±0.46abc       |
|                         | Large     | 4.25±0.00abc       | 7.09±0.34bc      | 8.63±0.27a         |
| Melatonin (n:8)         | Small     | 4.36±0.46abc       | 6.20±0.36bc      | 8.12±0.13abc       |
|                         | Large     | 5.03±0.56abc       | 8.76±0.36a       | 8.69±0.39a         |
| Cadmium (n:8)           | Small     | 4.68±0.51abc       | 5.84±0.53c       | 6.99±0.45d         |
|                         | Large     | 5.37±0.49a         | 6.32±0.27bc      | 7.39±0.22b         |
| Cadmium+Melatonin (n:8) | Small     | 3.56±0.28b         | 7.62±0.38abd     | 7.25±0.27c         |
|                         | Large     | 4.30±0.35abc       | 7.40±0.24b       | 8.48±0.06abc       |

a,b,c,d: The differences between average values indicated by different letters in the same column of the same parameters are important (p < 0.05)
oxidative stress formed is a suitable environment for the growth of harmful bacteria. A significant decrease was defined in the count of Lactobacillus spp. in both the small and large intestines in Cd group animals in present study. In addition, an important increase was detected in the Cd + Mlt group in both intestines in our study. It was also reported by Fazeli et al. (2011) that gram-positive basilus and enterococcus microorganisms were more sensitive to Cd toxicity than gram-negative Ecoli and Klepsiella species. These results can be explained by the fact that total bacterial rates of microflora varied with decreased count of Enterobacteriaceae due to Cd + Mlt administration or the high pH in the small intestine (Glombitza 2001; Marrero et al. 2004).

Lactobacillus spp. count was found lower in Cd group than C, Mlt and Cd + Mlt groups in small intestine microflora of the rats in our study. It has been reported by Fazeli et al. (2011) that Lactobacillus spp. count decreased due to different high doses of Cd treatment in small intestines of the mice which was corresponding with our results. Although decreased Lactobacillus spp. counts were detected by Fazeli et al. (2011) in large intestines depend on the different doses of Cd, it increased due to Mlt and Cd + Mlt treatments in large intestine of the rats except C group in our study. It was also reported that Mlt treatment increased the Lactobacillus spp. counts in large intestines of colitic mice which was consistent with present study (Zhu et al. 2018). It can be also expressed that Cd + Mlt treatment may be reduced Enterobacteriaceae count and lead to increase Lactobacillus spp./Lactococcus spp. rates, and/or activated the antioxidant system that can be confirmed by an increase in serum TAS levels in our study (Djurasevic et al. 2016).

CONCLUSION
Although Lactococcus spp. counts decreased 0.63 log in Cd group compared to C group in small intestine of the rats, it increased as 1.15 log in Cd + Mlt group. In addition, Cd + Mlt showed a lower antimicrobial effect on Lactococcus spp. than Cd in the small intestine. The effect of the Cd + Mlt treatment on lactic acid bacteries in the small intestine showed that Cd + Mlt chelate can be beneficial for intestinal microflora due to suppressed the Enterobacteriaceae growth, however ameliorated the Cd induced oxidative stress and Lactobacillus spp./Lactococcus spp. rates in the different part of the intestine.

CONFLICT OF INTEREST
The authors declare that they have no conflict of interest.

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