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Effects of Potassium Dichromate and Boron on Oxidative Stress and DNA Damage in Rats*,**

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Abstract: In this study, the effects of potassium dichromate ($K_2Cr_2O_7$) and boron (B, as boric acid) on oxidative stress and DNA damage in rat serum and liver were investigated. Sixty female Sprague-Dawley rats were divided into six groups of 10 animals each. The first group was kept as the control group. The second and third groups received 5 and 10 mg/kg B, respectively, the forth group received 10 mg/kg $K_2Cr_2O_7$, and the fifth and sixth groups received 5 and 10 mg/kg B plus $K_2Cr_2O_7$, respectively, orally for two weeks. Compared with the control groups, serum MDA levels increased ($P<0.01$) and TAC levels decreased ($P<0.001$) in the $K_2Cr_2O_7$ group. Serum MDA levels decreased in the $K_2Cr_2O_7$+5 and 10 mg/kg B groups, but a significant decrease was found in the $K_2Cr_2O_7$+10 mg/kg B group ($P<0.01$). Serum TAC levels showed a numerical increase in $K_2Cr_2O_7$+B groups. The liver MDA level was significantly decreased in the $K_2Cr_2O_7$+10 mg/kg B group compared to the other groups ($P<0.01$). There was no difference in plasma 8-OHdG levels between the groups. A positive correlation was observed between liver B and Cr levels ($P<0.05$). In this study, serum MDA and TAC levels were negatively affected in rats administered 10 mg/kg $K_2Cr_2O_7$. In contrast, administration of 10 mg/kg B to the $K_2Cr_2O_7$ group had positively effected on serum and liver lipid peroxidation indicators.
Keywords: Boron, DNA damage, oxidative stress, potassium dichromate, rat

Ratlarda Potasyum Dikromat ile Bor'un Oksidatif Stres ve DNA Hasarı Üzerine Etkileri

Öz: Bu çalışmada, sıçanlarda potasyum dikromat ($K_2Cr_2O_7$) ve borun (B, borik asit olarak) serum ve karaciğer oksidatif stres ve DNA hasarı üzerine etkileri araştırıldı. Altmış dişi Sprague-Dawley sıçan, her birinde 10 hayvan bulunan altı gruba ayrıldı. Birinci grup kontrol grubu olarak tutuldu. İkinci ve üçüncü gruplara sırasıyla 5 ve 10 mg/kg B; dördüncü gruba 10 mg/kg $K_2Cr_2O_7$; beş ve altıncı gruplara ise 5 ve 10 mg/kg B ile birlikte $K_2Cr_2O_7$ 2 hafta boyunca oral olarak verildi. Kontrol grupları ile karşılaştırıldığında $K_2Cr_2O_7$ grubunda serum MDA düzeyleri artarken ($P<0.01$), TAC düzeyleri azaldı ($P<0.001$). Serum MDA düzeyleri $K_2Cr_2O_7$+5 ve 10 mg/kg B gruplarında azaldı; ancak, anlamlı azalma $K_2Cr_2O_7$+10 mg/kg B grubunda ($P<0.01$) tespit edildi. Serum TAC düzeyleri $K_2Cr_2O_7$+B gruplarında sayısal artış gösterdi. Karaciğer MDA düzeyi, $K_2Cr_2O_7$+10 mg/kg B grubunda diğer gruplara göre anlamlı düzeyde azaldı ($P<0.01$). Gruplar arasında plazma 8-OHdG düzeyleri açısından fark belirlenemedi. Karaciğer B ve Cr düzeyleri arasında pozitif korelasyon saptandı ($P<0.05$). Bu çalışmada 10 mg/kg $K_2Cr_2O_7$ uygulanan ratlarda serum MDA ve TAC düzeyleri olumsuz etkilenirken, $K_2Cr_2O_7$ grubuna 10 mg/kg B verilmesi, serum ve karaciğer lipid peroksidasyon göstergeleri üzerine olumlu etki yaptığı söylenebilir.
Anahtar kelimeler: Bor, DNA hasarı, oksidatif stres, potasyum dikromat, rat

Introduction

Chromium (Cr) occurs at 0, 2^+, 3^+, and 6^+ oxidation states at the level of a metallic element and the 3^+ and 6^+ valance compounds are biologically most important (Mertz, 1969; Mc Dowell, 1992; Cohen et al., 1993; Barceloux, 1999; Zayed and Terry, 2003). All chemical forms of Cr, except chromates, can be removed quickly from the blood. The plasma Cr level is not a good indicator of the level of Cr in tissues since there is no balance between the levels of Cr in the tissues and circulation (Mc Dowell, 1992). The reticuloendothelial system shows a great affinity for Cr (Mertz, 1969); it has been reported that Cr is found to be less in blood, muscle, heart, lung, and brain compared to kidney, liver, pancreas, and spleen (Anderson and Polansky, 1995). Potassium dichromate ($K_2Cr_2O_7$) is an inorganic chemical substance generally used as an oxidizing agent in various laboratory and industrial areas (Danadevi et al., 2004; Patel et al., 2016). The Cr^{+6} is the most stable and strong oxidizing agent after Cr^{+3}, especially in the acidic environment. Hexavalent chromium binds oxygen as a chromate (CrO_7^{2-}) or dichromate ($Cr_2O_7^{2-}$) with a strong oxidative capacity (Mc Dowell, 1992; Nickens et al., 2010; Fedala et al., 2021; Orhan et al.,

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2022). Chromate ions (Cr^{+6}) can cross the cell membrane very quickly. In addition, the fact that chromates are very strong oxidants and irritants causes them to be more toxic than Cr^{+3}. Potassium dichromate is the most toxic form of Cr and is considered a carcinogen in humans and animals. It has been reported that the carcinogenic effect of CrO_7^{2-} ions causes DNA lesions and mutations (Mertz, 1969; Patlolla et al., 2009; Nickens et al., 2010; Patel et al., 2016). Excessive production of reactive oxygen species (ROS), which are produced during the reduction of Cr^{+5} and Cr^{+6}, reveals the toxic effects of Cr (Patlolla et al., 2009; Nickens et al., 2010; Patel et al., 2016; Bashandy et al., 2021; Fedala et al., 2021). Reactive oxygen species are also important for their toxic effects in that they damage macromolecules such as lipids, proteins, carbohydrates, and nucleic acids, disrupting the structure and function of cell membranes and causing cell death by inactivating enzymes (Nordberg and Arner, 2001; Klaunig et al., 2004).

Boron (B) is a dark brown nonmetal and is found in nature in the forms of borax (BX), colemanite, boronatrocalcite, and boric acid (BA) (Underwood and Suttle, 1999) and is widely used in industry (Butterwick et al., 1989). Although B was accepted to be essential for plants in 1923, it has recently been found that it may be an essential element for animals and humans (Mc Dowell, 1992; Nielsen, 1988; 1994). Although there is literature reporting that the amount of B that should be taken daily can vary between 0.5-1.0 mg in humans (Nielsen, 1991; WHO, 1996), there is no definite recommendation for humans and animals (NRC, 1994). Although it is thought that B can react with bio substances containing cis-hydroxyl groups (for example, glycolipids and phosphoinositides) and may be effective in the continuity of cell membrane functions or stability, hormone receptors, and transmembrane signals, its biochemical function in human and animal tissues is little known (Nielsen, 1990; 1991; Mc Dowell, 1992; Nielsen, 1994). Various studies have shown that B element is effective on bone, mineral, energy metabolism, immune and endocrine function and lipid peroxidation, antioxidant system and DNA damage (Türkez et al., 2007; İnce et al., 2010, 2012, 2014; Küçükkurt et al., 2015a,b, 2017; Acaröz et al., 2018, 2019; Çakır et al., 2018; İnce et al., 2019; Sarıca et al., 2019). Adequate literature has not been found regarding the effect of B element against oxidative stress caused by $K_2Cr_2O_7$ (Iztleuov et al., 2019, Sarıca et al., 2019). In this study, the effects of $K_2Cr_2O_7$, the most toxic form of Cr, and B element (as boric acid) on malondialdehyde (MDA), total antioxidant capacity (TAC), and DNA damage in serum/liver were determined in rats.

Material and Methods

Experimental design

Ethical approval for the study was obtained from the Erciyes University Animal Experiments Ethics Committee in Turkey (decision dated 11.04.2012 and numbered 12/56).

In the study, 60 female Sprague-Dawley rats were divided into six groups of ten. Control group (Group 1) rats were given 2 ml of distilled water; Groups 2 and 3 received 5 and 10 mg/kg (live weight)/day B, respectively; group 4 received 10 mg/kg $K_2Cr_2O_7$; 5th group 10 mg/kg $K_2Cr_2O_7$ + 5 mg/kg (live weight)/day B; group 6 also received $K_2Cr_2O_7$ + 10 mg/kg (live weight)/day B. Animals were given distilled water, $K_2Cr_2O_7$ and B (in the form of boric acid) by gavage for two weeks. The $K_2Cr_2O_7$ (Mohammed and Saber, 2011) and B (Price et al.1997) doses applied in this study were determined according to the results of previous studies. Researchers (Mohammed and Saber, 2011) stated that 10 mg/kg $K_2Cr_2O_7$ administration caused oxidative stress in their study in rats. The researchers (Price et al. 1997) determined that the addition of B up to 10 mg/kg (live weight) did not cause any adverse effects in rats, and negative effects began to be seen at doses above 10 mg, and the levels of NOAEL (No Observed Adverse Effect Level) that did not show any negative effects according to blood B levels were determined as 10 mg B/kg (bw). They reported that the low levels (LOAEL) at which signs of toxicity may develop were 13 mg B/kg, bw/day. Water and feed were given to the animals *ad libitum* throughout the experiment.

Collection of samples and biochemical analysis

At the end of the experiment, 2-3 ml of blood was taken from the animals as intra-cardiac (i.c.) into tubes with anticoagulant (Li-heparin) to determine 8-OHdG levels. The blood samples were centrifuged at 1300 x g for 10 minutes and their plasma was separated. To determine serum MDA, TAC, Cr, and B levels, 3-5 ml blood samples taken into tubes without anticoagulant were centrifuged at 1300 x g for 10 minutes and their serum was separated. In addition, liver tissue samples were taken to determine the tissue MDA level.

Serum/tissue MDA (Cayman, 10009055, USA), serum TAC (Rel Assay Diagnostics, RL 024, Turkey), and plasma 8-OHdG (NWK 8-OHdG 02, Northwest Life Science Specialist and LLC) analyses were measured in µQuant Bio-Tek ELISA reader using ELISA kit. Tissue B and Cr analyses were performed at Erciyes University Technology Research and Application Center on an ICP/MS (Agilent 7500a series) device.

Statistical analysis

Statistical analysis of the data was performed using the SPSS 20.0 package program for Microsoft. One-way analysis of variance (ANOVA) and Kruskal Wallis test were applied to determine the difference between groups. Data were analyzed with the Levene test for assumptions of homogeneity of variance and the Shapiro-Wilk test for assumptions of normal distribution (P>0.05). Duncan's Multiple Range Test and Bonferroni test were used to determine which group was responsible for the differences between the groups. Data were given as the mean and standard error of the means. The statistical significance level was determined as P<0.05. Spearman's Rho correlation coefficient was used for correlation analysis.

Results

In this study, compared to the control group, only the $K_2Cr_2O_7$ group had an increase in serum MDA level (P<0.01) and a decrease in the TAC level (P<0.001). Administration of 5 and 10 mg/kg B to the groups with $K_2Cr_2O_7$ decreased serum MDA levels, but a significant decrease was detected in the group given $K_2Cr_2O_7$ +10 mg/kg B (P<0.01). It was observed that the serum TAC levels increased numerically with the addition of B to the groups with $K_2Cr_2O_7$ (Table 1).

Table 1. Serum MDA, TAC, and plasma 8-OHdG levels in control, $K_2Cr_2O_7$, and B administered rats

Parameters	N	Control	5B	10B	$K_2Cr_2O_7$	$K_2Cr_2O_7$ +5B	$K_2Cr_2O_7$ +10B	P
MDA (nmol/mL)	8	5.18 ± 0.38^{bc}	5.32 ± 0.42^{bc}	5.55 ± 0.49^{bc}	7.49 ± 0.83^{a}	6.86 ± 0.48^{ab}	4.76 ± 0.57^{c}	**
TAC (mmol/L)	8	4.43 ± 0.29^{a}	4.25 ± 0.34^{abc}	4.33 ± 0.36^{ab}	2.64 ± 0.19^{d}	3.39 ± 0.18^{cd}	3.46 ± 0.34^{bcd}	***
8-OHdG (ng/mL)	8	0.277 ± 0.003	0.263 ± 0.007	0.272 ± 0.003	0.285 ± 0.008	0.270 ± 0.005	0.267 ± 0.004	-

$^{a-d}$: The difference between values with different letters on the same line is important.
5B: 5 mg/kg Boron, 10B: 5 mg/kg Boron
*-: Not significant, p>0.05; ** P<0.01; ***: P<0.001*

Liver MDA level showed a statistically significant decrease only in the $K_2Cr_2O_7$+10 mg/kg B group (P<0.01) compared to the other groups. The correlation coefficient between liver B and Cr levels was 0.556 and a positive correlation was found (P<0.05; Table 2).

Table 2. Liver MDA, B, and Cr levels in control, $K_2Cr_2O_7$, and B administered rats

Parameters	N	Control	5B	10B	$K_2Cr_2O_7$	$K_2Cr_2O_7$ +5B	$K_2Cr_2O_7$ +10B	P
MDA (nmol/mL)	8	9.50 ± 0.26^{a}	10.18 ± 0.19^{a}	9.80 ± 0.20^{a}	10.37 ± 0.56^{a}	8.45 ± 0.58^{ab}	7.38 ± 1.20^{b}	**
B (ppb)	7	0.13 ± 0.04^{d}	0.44 ± 0.02^{b}	0.51 ± 0.07^{b}	0.29 ± 0.02^{c}	1.96 ± 0.16^{a}	2.41 ± 0.28^{a}	***
Cr (ppb)	7	0.071 ± 0.003^{c}	0.59 ± 0.004^{c}	0.062 ± 0.005^{c}	0.919 ± 0.051^{b}	1.252 ± 0.025^{a}	1.239 ± 0.063^{a}	***

$^{a-c}$: The difference between values with different letters on the same line is important.
5B: 5 mg/kg Boron, 10B: 5 mg/kg Boron
*** P<0.01; ***: P<0.001*

Discussion and Conclusion

Hexavalent chromium (Cr^{+6}) is known to be a potential hepatotoxic and nephrotoxic agent associated with oxidative stress and inflammation (Patlolla et al., 2009; Patel et al., 2016; Navya et al., 2018; Orhan et al., 2022). In the study in which 2.5, 5, 7.5 and 10 mg/kg $K_2Cr_2O_7$ were applied to the diet in rats, it was determined that the MDA levels in both liver and kidneys increased significantly in the groups given 7.5 and 10 mg/kg $K_2Cr_2O_7$ compared to the control group (Patlolla et al., 2009). Likewise, in another study (Orhan et al., 2022), it was observed that administration of $K_2Cr_2O_7$ (15 mg/kg, i.p.) increased MDA levels, which is an indicator of lipid peroxidation, and decreased antioxidant enzymes in rat liver and kidney tissues. Bashandy et al. (2021) administered 10 mg/kg $K_2Cr_2O_7$ orally to rats for 8 weeks and found that glutathione, SOD, and CAT activities in testes decreased, while MDA and NO levels increased. These investigators suggested that the elevated MDA and NO levels in the testicles of rats exposed to $K_2Cr_2O_7$ were probably due to oxidative damage caused by the inability of antioxidant enzymes to scavenge oxidants produced in testicular tissue. Fedala et al. (2021) also administered the same dose of $K_2Cr_2O_7$ subcutaneously to pregnant Wistar albino rats and found that this substance supports hypothyroidism, oxidative stress, genotoxicity, and histological changes in the thyroid gland. Similarly, Patel et al. (2016) demonstrated the presence of genotoxicity and oxidative stress caused by $K_2Cr_2O_7$ (0.625, 1.25, and 2.5 mg/kg) toxicity was given orally by gavage for 28 days in Wistar rats. In another study (Navya et al., 2018), it was determined that 30 mg/kg $K_2Cr_2O_7$ given by gavage for 28 days in Wistar albino rats increased liver enzymes and TBARS levels in serum, decreased antioxidant enzymes in liver tissue, and it stated that increased toxic overload by reactive oxygen species may result in irregular expression in genes. An increase in the activity of lipid peroxidation was observed, possibly due to the formation of the hydroxyl radical catalyzed by chromium as indicated by Patel et al. (2016).

Ince et al. (2010), in their study on rats, found that

adding boric acid and borax to the diet (100 mg B/kg-live weight) significantly reduced the blood MDA level; they stated that there was a numerical decrease in MDA levels in the liver, kidney, and heart, which was not statistically significant, and that it also had positive effects on DNA damage. It has been reported that B can strengthen the antioxidant defense system of tissues by causing changes in oxidative metabolism through an undefined mechanism (Pawa and Ali, 2006; Çoban et al., 2015). In a study that produced hepatotoxicity with CCl_4 in mice; it has been stated that 50, 100 and 200 mg/kg (live weight) boric acid significantly reduces liver MDA levels and increases liver GSH, SOD and CAT activities. It has been stated that the hepatoprotective effect of boric acid may lead to both increased antioxidant defense system activity and inhibition of lipid peroxidation (İnce et al., 2012). Additionally, Türkez et al. (2007) found that 15 mg/L B component increased both SOD and CAT activities in erythrocytes, whereas 500 mg/L B decreased both SOD and CAT activities. On the other hand, Çakır et al. (2018) stated that 5 and 10 mg/kg B (i.p) reduced serum MDA levels in diabetic rats, but did not affect TAC levels. Acaroz et al. (2018) in their study on rats; showed that orally administered element B (5, 10, and 20 mg/kg) had a healing effect on oxidative stress and inflammation caused by acrylamide and alleviated tissue damage by preventing the decrease of antioxidant enzymes and suppressing lipid peroxidation. Likewise, the antioxidant, anti-inflammatory, and regulating effects of B (5, 10, and 20 mg/kg) in a dose-dependent manner on oxidative stress, inflammatory gene expression, metabolic and histopathological changes caused by Bisphenol A in rats have been revealed (Acaröz et al., 2019). Pawa and Ali (2006) 4 mg/kg of borax; Çoban et al. (2015) and Küçükkurt et al. (2017) also found that different doses of B (5, 10 and 20 mg/kg, respectively) may have positive effects on maintaining the oxidant/antioxidant balance in case of oxidative stress in rats in a dose-dependent manner.

Adequate literature has not been found regarding the effect of B element against oxidative stress caused by $K_2Cr_2O_7$ (Iztleuov et al., 2019, Sarıca et al., 2019). In a study (Iztleuov et al., 2019), the cardioprotective effects of orally administered 22.5 and 225 mg/kg sodium tetraborate on chromium intoxication ($K_2Cr_2O_7$), lipid profile correction, and oxidative stress were investigated. In this study, sodium tetraborate administered to rats at a level of 700 mg/L in their drinking water for 21 days increased both MDA levels and antioxidant system activity in the heart tissue, and it was revealed that lower doses had a positive effect on lipid peroxidation and antioxidant system. In a previous study we conducted on this subject, it was observed that lipid peroxidation in the brain tissue of rats treated with $K_2Cr_2O_7$ (10 mg/kg, i.p) decreased significantly after the application of 5 and 10 mg/kg B, but there was no significant change in antioxidant enzyme (SOD, CAT, and GSH-Px) levels (Sarıca et al., 2019).

In the presented study, it was observed that there was no statistical difference between the groups in terms of plasma 8-OHdG levels, but the plasma 8-OHdG level showed a numerical increase only in the $K_2Cr_2O_7$ group compared to the control. However, it was observed that the application of 5 and 10 mg/kg B to the $K_2Cr_2O_7$ groups caused a non-statistical numerical decrease in plasma 8-OHdG levels. Additionally, it was found that 5 and 10 mg/kg B given to groups with $K_2Cr_2O_7$ reduced serum MDA levels; and decreased liver MDA levels with statistical significance only in the group administered $K_2Cr_2O_7$ + 10 mg/kg B. It was also observed that serum TAC levels increased with the application of 5 and 10 mg/kg B to the $K_2Cr_2O_7$ groups, although not statistically. As a result, it was seen that B may have positive effects on oxidative stress and DNA damage caused by $K_2Cr_2O_7$ in rats. It was concluded that new research is needed in which different doses and compounds can be used to determine the exact effects of the boron element on metabolism.

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