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Ameliorating Effect of Ginger on Plasma Gonadotropin Hormones and Testosterone Hormones of Male Rats Exposed to Cadmium Toxicity

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ABSTRACT: This study was conducted to evaluate the effect of ginger supplementation on plasma gonadotropin and steroid hormones of rats exposed to oxidative stress. In a completely randomized design, 16 newly weaned rats were randomly allocated to four treatments. Treatments were as: control, ginger (500 mg/kg body weight), Cadmium at 2 mg/kg body weight and combination of Cadmium and ginger gavaged for 30-day trial period. Rats were anesthetized with diethyl ether and the blood was collected from heart by heparinized tubes. Administration of Cadmium increased significantly malondialdehyde concentration. Ginger supplementation could not decrease malondialdehyde significantly, but its level was numerically lower than those received Cadmium. Rats received control or ginger alone had lower plasma malondialdehyde concentration compared to those received Cadmium and there was no difference between them for malondialdehyde concentration. The lowest concentration was for those exposed to Cadmium toxicity and the highest was for rats received ginger. Administration of ginger could not improve the concentration of FSH in rats exposed to Cadmium toxicity. The highest concentration of LH was found for rats received ginger and the lowest was for those exposed to Cadmium alone. Administration of ginger for rats exposed to Cadmium toxicity increased numerically LH concentration. Administration of Cadmium decreased testosterone concentration ($P<0.05$) compared to control group. Ginger supplementation had no effect ($P<0.05$) on testosterone concentration compared to control group. Administration of ginger to rats exposed to oxidative stress could not improve the concentration of testosterone compared to group received ginger alone.

Keywords: Cadmium, Ginger, Gonadotrophin, Rat, Testosterone

INTRODUCTION

Cadmium accumulation within various tissues of the human and animals has been demonstrated in previous studies (Thompson and Bannigan, 2008; Liu *et al.*, 2010). The important target organs for this heavy metal are the hypothalamus (Lafuente *et al.*, 2001, Wang *et al.*, 2012) and testis (Siu *et al.*, 2009) and changes in neuroendocrine activity and sexual hormones production have been reported (Lafuente *et al.*, 1999). Acute Cadmium administration in male rats also results in severe impairment of testicular functions including germ cell death and inhibition of testicular steroidogenesis (Hew *et al.*, 1993; Yang *et al.*, 2003). Cadmium is known to deplete glutathione and protein-bound sulfhydryl groups, which results in enhanced production of reactive oxygen species (ROS) such as superoxide ion, hydroxyl radicals and hydrogen peroxide (Liu *et al.*, 2001).

When amount of free radicals reach more than antioxidant capacity (enzymatic and non-enzymatic), oxidative stress can be occurred and malondialdehyde as sign of oxidative stress and lipid peroxidation increased as their level reach in measurable range in blood. Oxidative stress causes damage to biologic macromolecules (such as nucleic acids, membrane lipids and proteins) and disorder of normal metabolism and physiology especially hormone production and release (Roberts and Sindhu, 2009).

The use of ginger as an important herbal medicine has antioxidative properties and scavenges oxidative stress (Kota *et al.*, 2008; Mallikarjuna *et al.*, 2008). The effects of ginger as an antioxidant on many biological parameters (Afshari *et al.*, 2007; Kota *et al.*, 2008; Mallikarjuna *et al.*, 2008) in non-stressed condition have been studied, but its effect on gonadotropinal and steroidal hormones in the stress condition remains also unclear.

We hypothesized that ginger is capable to prevent the adverse effects of oxidative stress on gonadotropic and steroidal hormones in female rats. Therefore, the present study was carried out to investigate the effects of oxidative stress induced by Cadmium, and also the effects of ginger, alone or together with oxidative stress, on the concentration of gonadotropic and steroidal hormones in male rats.

MATERIAL AND METHODS

The research was conducted in Islamic Azad University (Science and Research Branch), Iran. Sixteen newly weaned male Wistar rats (55-60 g body weight) were obtained from the Pasteur Institute (Tehran, Iran). The rats were maintained under controlled conditions of a 12 h light–dark cycle, room temperature of 22-25 °C, relative humidity of 40–50%. Rats were allowed free access to standard rat chow diet and water. After one week of acclimatization to the laboratory conditions, rats were randomly divided into four experimental groups (4 rats in each) as follows: The first group served as normal control group and was injected phosphate saline buffer. Rats of the second group were treated with ginger at a dose of 500 mg/kg body weight five times per week for 4 weeks. The third group was intoxicated with 2 mg/kg body weight Cadmium five times per week for 4 weeks. The fourth group was treated with both Cadmium and ginger. The Cadmium and ginger was dissolved in sterilized distilled water and both were gavaged. Ginger treatment started 1 week before Cadmium administration and continued throughout the duration of the experiment. The doses of Cadmium and ginger were calculated according to the animal's body weight before each administration. All rats were handled in accordance with the standard guide for the use and care of laboratory animals. At the end of the experimental duration, rats were fasted overnight with free access to water. Rats were anesthetized with diethyl ether and blood was collected into heparinized tubes from heart. The blood was then centrifuged and the plasma was collected and kept at -20 °C for the determination of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone.

Hormones of LH, FSH and testosterone were measured using enzyme-linked immunosorbent assay (ELISA) kits. Briefly, this assay employs the competitive inhibition enzyme immunoassay technique. The micro titer plate provided in these kits had been pre-coated with goat-anti-rabbit antibody. Standards or samples were added to the appropriate micro titer plate Horse Radish with an antibody specific for hormone and Horseradish Peroxidase (HRP) conjugated hormone. The competitive inhibition reaction was launched between with HRP labeled hormone and unlabeled hormone with the antibody. A substrate solution was added to the wells and the color develops in opposite to the amount of hormone in the sample. The color development was stopped and the intensity of the color measured.

Data were subjected to analysis of variance procedures appropriate for a completely randomized design using the General Linear Model procedures of SAS software. Mean comparison was done using the Duncan's Multiple Range Test at $P < 0.05$.

RESULTS

The effect of different treatments on plasma malondialdehyde concentration is shown in Fig. 1.

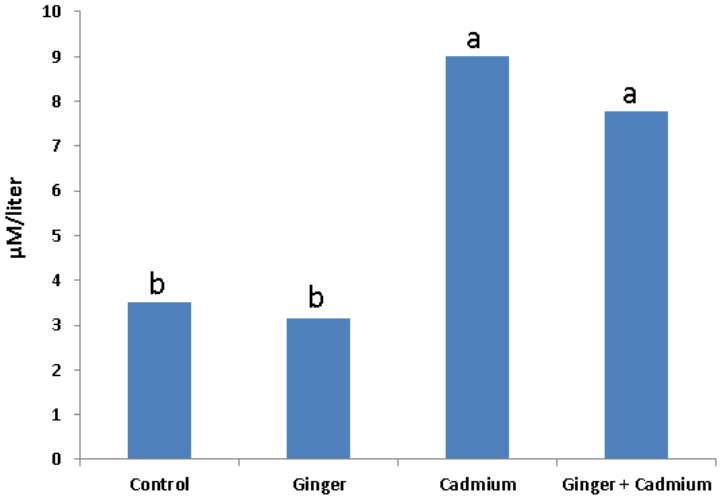

Fig. 1. Effect of different treatments on plasma malondialdehyde concentration.

Administration of Cadmium (treatment 3) increased significantly malondialdehyde concentration. Ginger supplementation could not decrease malondialdehyde significantly, but its level was numerically lower than treatment 3. Rats received control or ginger alone had lower plasma malondialdehyde concentration compared to those received Cadmium and there was no difference between them for malondialdehyde concentration.

The effect of Cadmium and ginger administration on FSH concentration is shown in Fig. 2. The lowest concentration was for those exposed to Cadmium toxicity and the highest was for rats received ginger. Administration of ginger could not improve the concentration of FSH in rats exposed to Cadmium toxicity. The effect of Cadmium and ginger administration on LH concentration is shown in Fig. 3. There were significant differences among treatments for LH concentration. The highest concentration of LH was found for rats received ginger and the lowest was for those exposed to Cadmium alone. Administration of ginger for rats exposed to Cadmium toxicity increased numerically LH concentration.

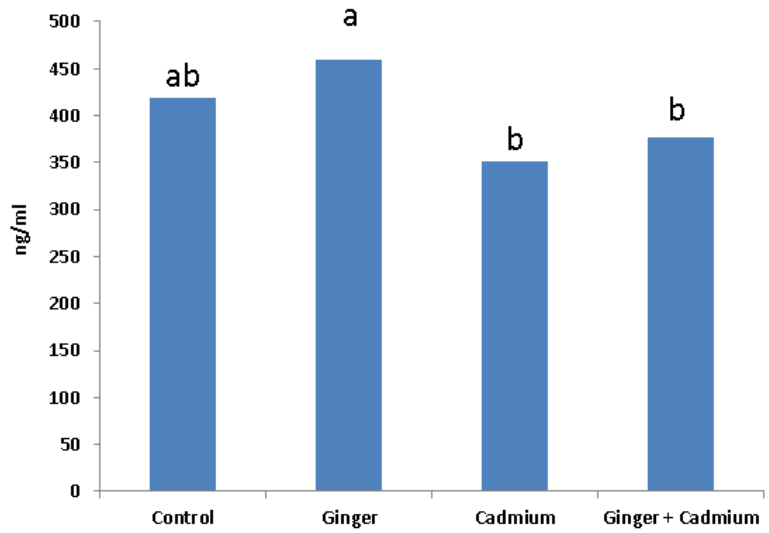

Fig. 2. Effect of different treatments on plasma FSH concentration.

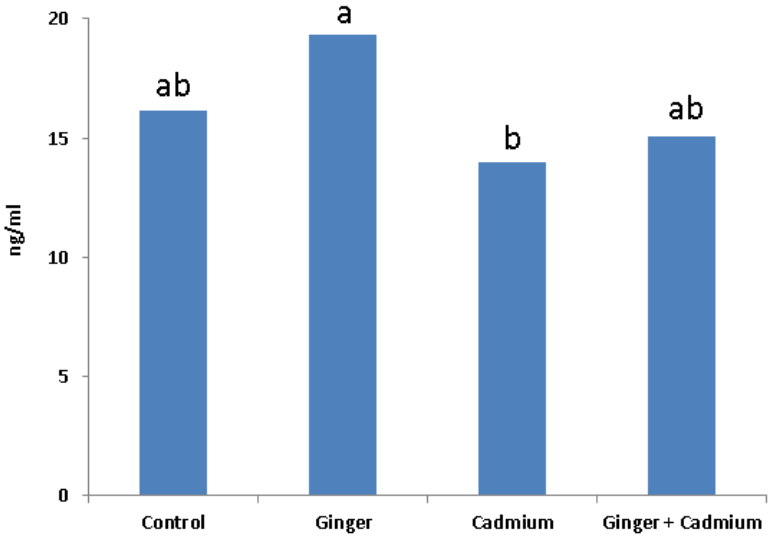

Fig. 3. Effect of different treatments on plasma LH concentration.

There were significant differences among treatments for testosterone concentration (Fig. 4). Administration of Cadmium decreased testosterone concentration ($P < 0.05$) compared to control group. Ginger supplementation had no effect ($P < 0.05$) on testosterone concentration compared to control group. Administration of ginger to rats exposed to oxidative stress could not improve the concentration of testosterone compared to group received ginger alone.

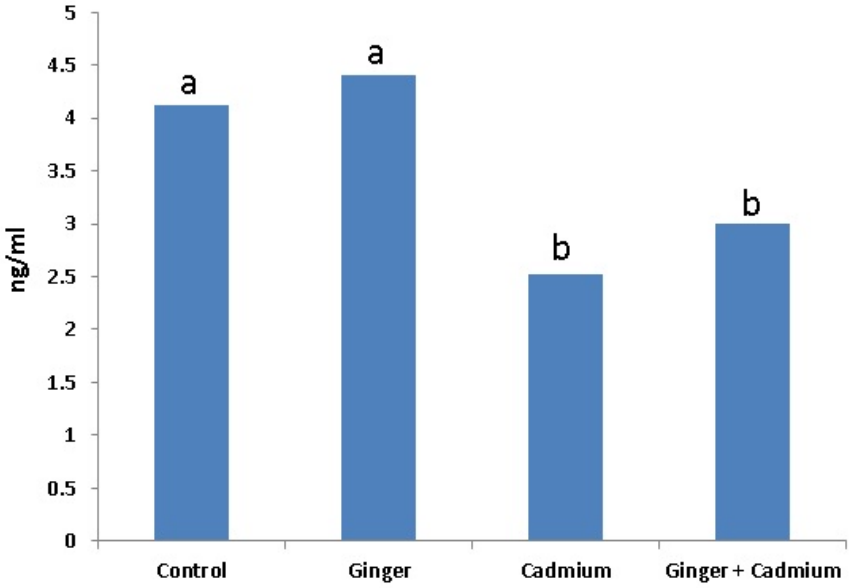

Fig. 4. Effect of different treatments on plasma testosterone concentration.

DISCUSSION

Our experimental data showed that plasma malondialdehyde concentration in rats received Cadmium was significant higher than those of the control group, which suggests that oxidative stress may be a contributing factor. Malondialdehyde is formed as an end product of lipid peroxidation. Oxidative stress induced by Cadmium is believed to be one of important factors in hypothalamus, pituitary gland and testicular damages (Tremellen, 2008; Turner and Lysiak, 2008). Based on our results and other studies, multiple possible mechanisms exist by which Cadmium induces oxidative stress affects the gonadotropin and steroid hormones from their glands. The first mechanism involves the depletion of glutathione content. Glutathione, an important non-enzymatic antioxidant, can accept two electrons from free radicals, thus oxidizing to form oxide glutathione under the action of glutathione peroxidase. Through this action, glutathione could inactivate the destructive effects of the free radical. After production, oxide glutathione obtains two protons from NADPH and converts back to glutathione under the action of glutathione reductase, thus forming an antioxidant cycle. It was reported (Lafuente *et al.*, 2005) that Cadmium inhibits the activity of glutathione peroxidase and glutathione reductase, which indicates this heavy metal can promote depletion of glutathione and inhibit production of it. The other mechanism by which Cadmium can induce oxidative stress is through inhibition of antioxidant enzyme activity. Superoxide dismutase, an important enzymatic antioxidant, lies in cytoplasm and mitochondrion. It was reported (Lafuente *et al.*, 2005) that the superoxide dismutase activity was significantly decreased by Cadmium treatment, which indicates Cadmium can inhibit superoxide dismutase activity. The interaction of Cadmium and Zinc may also cause the testicular zinc content to decrease, which also decreases superoxide dismutase activity (King *et al.*, 1999).

The rats received ginger compare those in Cadmium toxicity indicated that lipid peroxidation was reduced by ginger via enhancing antioxidative action, but its effect was not significant.

There is a report indicated that reduction of malondialdehyde concentration in the plasma could partially be attributed to an increase in antioxidant enzymatic activity associating with ginger supplementation, and also this result agree with some reports (Bayraktar *et al.,* 2011; Erdouan *et al.,* 2005). These researches reported that ginger has antioxidant activity in chicks on lipid peroxidation; also they found the use of antioxidant additive in chick diets can prevent the oxidative stress and a decrease in malondialdehyde as lipid peroxidation markers. Ginger contains many of compounds that had biological activities, including antioxidant (Nakatani, 2000; Rababah *et al.,* 2004), antimicrobial (Akoachere *et al.,* 2002; Mahady et al., 2003), and various pharmacological effects (Chrubasik *et al.,* 2005; Ali *et al.,* 2008). Ginger has long been used to alleviate the symptoms of gastrointestinal illnesses as traditional medicine (Afzal *et al.,* 2001). Ginger has been found to enhance pancreatic lipase activity (Platel *et al.,* 1996). The potential active constituents in ginger are the gingerols, shogaols, gingerdiol, gingerdione, and some related phenolic ketone derivatives (Kikuzaki *et al.,* 1996; Fuhrman *et al.,* 2000). In our study ginger alone improved production of hormones, but it cannot ameliorate the Cadmium toxicity effect on gonadotrophin and steroid hormones in rats.

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