Malathion-induced testicular toxicity in male rats and the protective effect of vitamins C and E

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1. Introduction

Organophosphorus compounds are widely used in agriculture as insecticides and acaricides. They are also frequently employed in medicine and industry. Residual amounts of organophosphate (OP) pesticides have been detected in the soil, water bodies, vegetables, grains, and other food products (IARC, 1983; Poet et al., 2004). Moreover, due to the wide availability of organophosphorus compounds, poisonings are common (Garcia et al., 2003). OP pesticides are known to inhibit acetylcholinesterase and pseudocholinesterase activity in target tissues (John et al., 2001; Kalender et al., 2006). Other systems that may be affected by OP exposure are the immune system (Handy et al., 2002), pancreas (Gokalp et al., 2005), liver (Kalender et al., 2005), and hematological system (Kalender et al., 2006). Some OP pesticides have also been reported to affect the reproductive system (Farag et al., 2000).

Malathion [O,O-dimethyl-S-[1,2-dicarbethoxyethyl] phosphorodithioate] is an OP pesticide that is widely used in agricultural and household applications to control pests. Malathion is also extensively used for mosquito eradication and as an animal ectoparasiticide and human miticide (Elston, 2002; Roberts, 2002; Suresh Babu et al., 2006). The widespread use of malathion and the high rates of food contamination could lead to humans, animals, and birds being exposed to high levels of this pesticidal chemical (Suresh Babu et al., 2006). Malathion is known to inhibit acetylcholinesterase activity in target tissues (Rezg et al., 2008a,b) and has been found to affect the mammalian reproductive system. For example, mice treated with intraperitoneally-injected malathion show significantly higher frequencies of abnormal sperm (Contreras and Bustos-Obregón, 1999). Moreover, malathion exposure has been shown to significantly decrease the sperm count of mice (Bustos-Obregón and Gonzáles-Hormazabal, 2003).

Many insecticides are hydrophobic molecules that bind extensively to biological membranes, especially phospholipid bilayers (Lee et al., 1991), and they may damage the membranes by inducing lipid peroxidation. Since vitamins C and E are known to be antioxidants, a number of studies have been performed to determine whether they can ameliorate the toxic effects of pesticides (Kalender et al., 2006, 2007; Uzunhisarcikli et al., 2007; Ogutcu et al., 2008). Vitamin E (α-tocopherol) is the major lipid-soluble antioxidant and is known to protect cellular membranes and lipoproteins from peroxidation (Yavuz et al., 2004). Moreover, several studies have shown that α-tocopherol inhibits free radical...
formation (Kalender et al., 2004) and may effectively minimize lipid peroxidation in biological systems (Traber and Atkinson, 2007). Vitamin C (ascorbic acid) is a low molecular weight antioxidant that defends the cellular compartment against water-soluble oxygen nitrogen radicals. It is an effective antioxidant of the hydrophilic phase (Jurczuk et al., 2007). Moreover, vitamin C can restore the antioxidant abilities of vitamin E, which suggests that a major function of ascorbic acid is to recycle the tocopherolyl radical (Serbecic and Beutelspacher, 2005).

The aim of this study was to determine the effect of subacute malathion exposure on the reproductive system of male rats and to assess whether these effects can be ameliorated by co-treatment with vitamins E and C. To achieve this aim, rats were given malathion and/or vitamins E and C by oral gavage for 4 weeks, after which their sperm counts, sperm motility, sperm morphology, and hormone levels were assessed and their testes were examined for pathological changes.

2. Material and methods

2.1. Animals

Sexually mature male Wistar rats (weighing approximately 300–320 g) obtained from the Gazi University Laboratory Animals Growing and Experimental Research Center were used. The animals were housed in plastic cages, fed a standard laboratory diet and water ad libitum, and maintained at a laboratory temperature of 20 ± 2 °C. The animals were quarantined for 10 days before beginning the experiments. All rats were handled in accordance with the standard guide for the care and use of laboratory animals.

2.2. Chemicals

Malathion was obtained from the Agricultural Struggle Center, Ankara, Turkey. Vitamin E (DL-α-tocopherol acetate) was supplied by Merck (Germany). Vitamin C (L-ascorbic acid) was supplied by Carlo Erba (Milano, Italy).

2.3. Animal treatment schedule

The rats were divided into two groups, namely, the control (n = 6) and experiment groups (n = 18). The rats in the experiment group were divided into three groups, namely, the vitamins C and E-treated group (vitamin-treated group) (n = 6), the malathion-treated group (n = 6), and the vitamin plus malathion-treated group (n = 6). The substances were administered in the morning (between 09:00 and 10:00 h) to non-fasted rats. The first day the animals were treated was accepted as the experimental day 0. At the end of the 4th week (28 days) of treatment, the six rats in each group were sacrificed and dissected, and tissue samples were taken to determine testicular sperm counts, epididymal sperm motility, and epididymal sperm morphology. These samples were also subjected to light microscopy investigations. Blood samples were collected for assaying the levels of plasma hormones, including luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone.

2.3.1. Control group

Corn oil at a dose of 0.2 ml per animal was given via gavage, once a day.

2.3.2. Vitamins C and E-treated group (Vitamin-treated group)

Vitamins C and E were dissolved in water and corn oil, respectively. Once a day, the rats were treated, via gavage, with first vitamin C (200 mg/kg bw per day) and then vitamin E (200 mg/kg bw per day).

2.3.3. Malathion-treated group

Once a day, the rats were given malathion at a dose of 27 mg/kg bw (1/50 of the LD₅₀ for an oral dose) per day in corn oil via gavage.

2.3.4. Vitamin plus malathion-treated group

Once a day, the rats were given vitamin C dissolved in water (200 mg/kg bw per day) and vitamin E dissolved in corn oil (200 mg/kg bw per day) by gavage, and 30 min later, malathion dissolved in corn oil (27 mg/kg bw per day) was administered via gavage.

2.4. Testicular sperm count

One testis of each rat was placed in 1 ml of phosphate buffer saline immediately after dissection. The tunica albuginea was cut by surgical blades and removed, and the remaining seminiferous tubules were mechanically minced by using surgical blades in 1 ml of phosphate buffer saline. The testicular cell suspension was pipetted several times to form a homogenous cell suspension. One drop of the suspension was placed on a “Makler Counting Chamber” (Sefi Medical Instruments, Israel) and the testicular sperm concentration was determined under a phase contrast microscope at 200× magnification and expressed as million sperm cells per ml of suspension.

2.5. Sperm motility analysis

The sperm were collected as quickly as possible after a rat was sacrificed. The cauda epididymis was placed in 1 ml of 37 °C phosphate buffer saline solution and cut by surgical blades into approximately 1 mm³ pieces. The solution was pipetted several times to homogenize the sperm suspension. One drop of the suspension was placed on a slide, covered by a 24 × 24 mm coverslip, and evaluated under a phase contrast microscope at 200× magnification. The sperm were categorized on the basis of their motility as “motile” or “immotile.” The results were recorded as percentage of sperm motility.

2.6. Epididymal sperm morphology

After evaluating epididymal sperm motility, the sperm suspension was used for the analysis of sperm morphology. Thus, one drop of the suspension was smeared onto a glass slide and stained by the commercial ready-to-use “Sperm” stain. In total, 2000 sperm on each slide were evaluated and the results were recorded as the percentage of abnormal sperm on each slide. Abnormal heads and tails were evaluated by using the criteria of Nahas et al. (1989), Mori et al. (1991) and Okamura et al. (2005).

2.7. Hormone assays

LH and FSH levels in the plasma were measured by using automated immunofluorescent assay-based commercial kits and a Brahms Kryptor immunoassay analyzer (Brahms LH Kryptor 820.050 and Brahms FSH Kryptor 818.050, respectively). The testosterone levels were measured by using a chemiluminescence immunosay-based commercial kit (Access testosterone 33,560) and an Access immunoassay analyzer (Beckman Coulter).

2.8. Histopathology

For histopathological examination, the testicular tissues were dissected and the tissue samples were fixed in Zenker solution for 24 h, processed by using a graded ethanol series, and embedded in paraffin. The paraffin sections were cut into 5 μm-thick slices and stained with hematoxylin and eosin for light microscopic examination. The sections were viewed and photographed by using an Olympus light microscope (Olympus BX51, Tokyo, Japan) with an attached photograph machine (Olympus E-330, Olympus Optical Co. Ltd., Japan).

2.9. Statistical analysis

The data were analyzed by using SPSS 11.0 for Windows. The significance of differences was calculated by using one-way analysis of variance (ANOVA) followed by Tukey’s procedure for multiple comparisons (Montgomery, 1997). P < 0.05 was considered statistically significant.

3. Results

3.1. Evaluation of testicular sperm counts

The vitamin-treated group did not differ significantly from the control group at the end of the 4th week in terms of sperm counts, but the malathion- and vitamin plus malathion-treated rats had significantly lower sperm counts than the control group (P < 0.05; Table 1). However, the vitamin plus malathion-treated rats had significantly higher sperm counts than the malathion-treated group (P < 0.05; Table 1).

3.2. Evaluation of sperm motility

The vitamin-treated rats did not differ significantly from the control rats in terms of their total epididymal sperm motility at the end of the 4th week, but the malathion- and vitamin plus malathion-treated rats had significantly lower sperm motility than the control rats (P < 0.05; Table 1). However, the vitamin plus mala-
than the control rats (Table 2). However, the vitamin plus malathion-treated rats had significantly lower plasma FSH, LH and testosterone levels at the end of the 4th week compared to the malathion-treated and vitamin plus malathion-treated rats (Table 2). In contrast, after 4 weeks of vitamin plus malathion treatment, the vitamin-treated group and control rats were structurally normal (Fig. 1A and B). Leydig cells were found in the interstitial connective tissue between the seminiferous tubules of the vitamin-treated group and control rats, while spermatozoa were lined by regularly arranged rows of spermatogenic cells at different stages of maturation (Fig. 1A). These changes are concentration-dependent and intensify with longer periods of exposure (Farag et al., 2000; Khan et al., 2001; Uzunhisarcikli et al., 2007). Moreover, after 4 weeks of vitamin plus malathion treatment, there were fewer spermatogenic cells in some of the seminiferous tubules and mild edema in the interstitial tissues (Fig. 1D).

4. Discussion

Malathion is a widely used pesticide that affects a variety of organisms. Epidemiological research into the acute and chronic toxicity of malathion indicates that this chemical is highly toxic to mammals (Abdollahi et al., 1999). Mammals are expected to be adversely affected by oral, dermal and inhalation exposure to malathion (Brand et al., 2005; Rezg et al., 2008b; Lasram et al., 2008; Edwards et al., 2007). Malathion not only has toxic effects on mammals, it also has toxic effects on fish, chicks and non-target invertebrates (Senger et al., 2005; Sodhi et al., 2008). The oral LD50 of malathion for male rats is 1350 mg/kg (John et al., 2001). However, when Rezg et al. (2008a) gave rats 100 mg/kg malathion intragastrically, they observed hepatic damage and biochemical changes. In the present study, even though malathion was given at 1/50 of the oral LD50, we observed pathological changes in rat testes, although none of the rats died during the experimental period. It has been shown that pesticides can cause various histopathological and cytopathological changes in the reproduction system of male mammals (Mahgoub and El-Medany, 2001; Uzunhisarcikli et al., 2007). These changes include decreased spermatogenesis and sperm counts. For example, acephate, an OP insecticide, decreases the number of spermatogenic cells in the testes (Falag et al., 2000), while Khan et al. (2001) reported that phosphorothionate, an OP insecticide, inhibits spermatogenesis. In addition, Xu et al. (2004) have found that male rats exposed to phoxim, an OP insecticide, along with fenvalerate, a pyrethroid insecticide, showed decreased daily sperm production. In addition, OP insecticides not only decrease sperm counts, they also reduce sperm motility (Falag et al., 2000; Khan et al. 2001; Uzunhisarcikli et al., 2007). Moreover, pesticide-exposed experimental animals produce significantly higher numbers of dead or abnormal sperm (Buret et al., 2000; Uzunhisarcikli et al., 2007; Contreras and Bustos-Obregón, 1999). These changes are concentration-dependent and intensify the longer the animals are exposed. That malathion exposure also reduces sperm counts has been shown previously by Contreras and Bustos-Obregón (1999), who found that mice treated intraperitoneally for 18 days with male rats exhibited decreased sperm counts. Uzunhisarcikli et al. (2007) also found rats exposed for 4 and 7 weeks to a close relative of malathion, methyl parathion, had decreased sperm counts. Malathion and methyl parathion have also been reported to reduce sperm motility and viability, and to increase abnormal sperm numbers (Uzunhisarcikli et al., 2007; Contreras and Bustos-Obregón, 1999). In the present study, we also observed that rats had lower sperm counts after 4 weeks of malathion treatment by gavage. Similarly, these rats exhibited a significant decrease in sperm motility and increased abnormal morphology rates.

It is likely that these effects of malathion and other OPs relate, at least in part, to their ability to cross the blood–testis barrier (Uzunhisarcikli et al., 2007), after which they induce oxidative stress and lipid peroxidation that damages the biological mem-

### Table 1
Subacute effect of malathion on sperm motility, sperm morphology and abnormal sperm morphology in rats.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Sperm count (million/mL)</th>
<th>Sperm motility (%)</th>
<th>Abnormal sperm morphology (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>28.43 ± 0.94</td>
<td>71.93 ± 1.27</td>
<td>1.71 ± 0.05</td>
</tr>
<tr>
<td>Vitamins C and E</td>
<td>27.05 ± 1.30</td>
<td>72.40 ± 2.27</td>
<td>1.67 ± 0.04</td>
</tr>
<tr>
<td>Malathion</td>
<td>22.11 ± 1.17ab</td>
<td>45.83 ± 1.38ab</td>
<td>2.72 ± 0.06ab</td>
</tr>
<tr>
<td>Vitamins C and E + malathion</td>
<td>24.68 ± 0.75ab</td>
<td>53.58 ± 1.01ab</td>
<td>1.97 ± 0.10ab</td>
</tr>
</tbody>
</table>

Values are mean ± SD of six rats in each group. Significance at P < 0.05.

<sup>a</sup> Comparison of control and other groups.

<sup>b</sup> Comparison of vitamin-treated group with malathion- and vitamin plus malathion-treated groups.

<sup>c</sup> Comparison of malathion-treated group with vitamin plus malathion-treated group.

### Table 2
Subacute effect of malathion on plasma levels of FSH, LH and testosterone in rats.

<table>
<thead>
<tr>
<th>Groups</th>
<th>FSH (mIU/ml)</th>
<th>LH (mIU/ml)</th>
<th>Testosterone (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>3.19 ± 0.03</td>
<td>1.29 ± 0.06</td>
<td>3.92 ± 0.09</td>
</tr>
<tr>
<td>Vitamins C and E</td>
<td>3.15 ± 0.03</td>
<td>1.24 ± 0.04</td>
<td>3.86 ± 0.07</td>
</tr>
<tr>
<td>Malathion</td>
<td>2.64 ± 0.17ab</td>
<td>0.88 ± 0.04ab</td>
<td>2.86 ± 0.04ab</td>
</tr>
<tr>
<td>Vitamins C and E + malathion</td>
<td>2.67 ± 0.05ab</td>
<td>0.90 ± 0.01ab</td>
<td>2.94 ± 0.05ab</td>
</tr>
</tbody>
</table>

Values are mean ± SD of six rats in each group. Significance at P < 0.05.

<sup>a</sup> Comparison of control and other groups.

<sup>b</sup> Comparison of vitamin-treated group with malathion- and vitamin plus malathion-treated groups.
branes in the testes. This in turn may cause the degeneration of the spermatogenic and Leydig cells, which disrupts spermatogenesis and reduces sperm counts. Supporting this is the fact that we found that subacute exposure to malathion-induced histopathological changes in the seminiferous tubules, namely, necrosis and edema in the seminiferous tubules and interstitial tissue. The sperm themselves may also be damaged by the oxidative effects of OPs, which affect the activities of mitochondrial enzymes and the structure of the microtubules in the sperm. This in turn reduces their motility. That reactive oxygen species may contribute to infertility caused by defective sperm function has been reported previously (Latchoumycandane et al., 2002). Another way OPs affect male reproductive function is to damage DNA (Sarabia et al., 2009). Increases in abnormal sperm counts and the disruption of spermatogenesis are important indicators of genetic damage in pesticide-exposed mammals (Burruel et al., 2000). Since sperm morphology is controlled by various autosomal and Y-specific genes (Forejt, 1976; Krazanowska, 1976), DNA damage may also reduce sperm motility.

Supporting the notion that OPs like malathion exert their deleterious effects by promoting destructive oxidation of lipids, proteins and DNA within the testis is our finding that co-treatment of malathion-exposed rats with vitamins E and C ameliorated the effects of malathion on sperm counts, motility and morphology, and the integrity of the testis. Uzunhisarcıklı et al. (2007) have also reported that administration of vitamins C and E improves sperm counts, motility, and morphology. Antioxidant vitamins have a number of biological activities, including immune stimulation and alteration of the metabolic activities of carcinogens. These vitamins can also prevent genetic changes by inhibiting the DNA damage induced by reactive oxygen metabolites (Verma et al., 2007). Vitamin E is a lipid-soluble vitamin that is present in biological membranes (Senthil Kumar et al., 2004). It efficiently protects against lipid peroxidation through its chain-breaking antioxidant activity (Serbecic and Beutelspacher, 2005), wherein vitamin E is converted to a weak free radical (the α-tocopherol radical) (Zaken et al., 2001). Vitamin C (ascorbic acid) is hydrophilic and functions better in an aqueous environment. Moreover, it can restore the antioxidant properties of oxidized tocopherol, which suggests that a major function of ascorbic acid is to recycle the tocopheroxyl radical (Serbecic and Beutelspacher, 2005).

Finally, OPs may also affect male reproductive function by decreasing FSH, LH and testosterone levels. Significant alterations in FSH, LH and testosterone levels have been reported after exposure to certain pesticides (Elbetieha and Da’as, 2003; Maitra and Mitra, 2008). For example, exposure to methyl parathion has been reported to significantly reduce LH and testosterone levels (Maitra and Mitra, 2008). However, other researchers have found that pesticides elevate FSH and LH levels (Mahgoub and El-Medany, 2001). LH and FSH activity depends on both the quantity of these hormones and the number of specific receptors in the testis. It has been shown that exposure to environmental contaminants adversely affects testicular function by decreasing pituitary LH secretion and reducing Leydig cell steroidogenesis (Akingbemi et al., 2004; Murugesan et al., 2007). In our study, the FSH and LH levels in the malathion-treated rats were significantly lower than the levels in the control rats at the end of the 4th week. Thus, subacute malathion exposure suppressed FSH and LH secretion. Notably, however, co-treatment with vitamins C and E did not have a protective effect on FSH and LH levels. These results may be explained by the putative androgen receptor antagonistic property of malathion: it is known that androgen receptor antagonist substances can alter the glycosylation of gonadotrophins, which results in the suppression of FSH and LH levels (Naz, 1999).

Together with gonadotrophins, testosterone is a key hormone that regulates spermatogenesis. The secretion of testosterone by the Leydig cells is dependent upon the secretion of LH by the pituitary gland. Various OPs have been studied for their effect on testosterone levels. Quinalphos treatment was shown to significantly reduce the plasma concentration of testosterone and the...
testicular testosterone levels (Ray et al., 1992). However, Okamura et al. (2005) did not observe that OPs significantly change plasma testosterone levels. In this study, malathion exposure for 4 weeks was associated with a decrease in plasma testosterone levels. This may be because malathion induces pathological changes in the Leydig cells in the interstitial tissues.

Thus, in summary, in this study, we found that a low dose of malathion causes testicular toxicity, but that the antioxidant vitamins C and E are protective in terms of sperm counts, motility and morphology. However, they do not protect malathion-exposed rats from the effects of malathion on FSH, LH and testosterone levels.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

Acknowledgements

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