Effects of Malathion on Humoral Immunity and Macrophage Function in Mast Cell-Deficient Mice

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Malathion is an organophosphate pesticide which has a low mammalian toxicity due to detoxification of malathion into nontoxic derivatives by carboxylesterases (Aldridge et al., 1979; Dauterman, 1971; Frawley et al., 1957; March et al., 1956; Umetsu et al., 1977, 1981). Because of this low toxicity, malathion is used in situations where large urban populations and domesticated animals may be exposed (Weeks et al., 1977).

Such situations include mosquito eradication, spraying of tobacco plants, and aerial spraying for the eradication of fruit flies in citrus-producing states. One published study by Milby and Epstein (1964) has suggested that malathion may cause contact dermatitis (immune hypersensitivity) in human populations. In this study, 43% of persons exposed to technical malathion under an occlusive patch for 48 hr developed contact dermatitis upon reexposure. Due to the brevity of technical information in this publication, the ability of malathion to cause rash formation after the first exposure or during shorter exposures is not known. In addition, the study design did not distinguish between a direct effect of malathion on the mast cell or an indirect effect through the generation of an immune response to malathion.

Animal studies have shown that acute administration of noncholinergic doses of purified malathion elevated the humoral immune and proliferative response to mitogenic stimuli (Rodgers et al., 1986; Rodgers and Ellefson, 1990). The increase in proliferative responses to mitogen was shown to be due to alterations in the adherent cell population (Rodgers and Ellefson, 1990). Further studies indicated that acute, oral administration of malathion to mice or in vitro exposure of mouse or human white cells to metabolized malathion increased the respiratory burst of leukocytes stimulated by phorbol esters (Rodgers and Ellefson, 1990). More recently, it was shown that administration of very low doses of malathion increased macrophage function as measured by respiratory burst function and phagocytosis (Rodgers and Ellefson, 1992). These studies also showed that in vivo administration of malathion led to degranulation of peritoneal mast cells. Most recently, it was shown that in vitro exposure of purified mast cells or a basophilic tumor cell line to metabolites of malathion resulted in the release of mast cell mediators (Xiong and Rodgers, submitted). This study confirms that malathion, particularly metabolized malathion, can cause the degranulation of basophilic cells. These data suggest that the observations made by Milby and Epstein (1964) may be the result of direct degranulation of mast cells by malathion rather than through the generation of a specific immune response.

Published reports indicate that mast cell mediators, which include cytokines, lipid-derived mediators, histamine, hep-
MATERIALS AND METHODS

Animals and Mast Cell Reconstitution

**Mice.** Mast cell-deficient female mice, WBB6F1-W/W (W/W) or WCB6F1-SI/Sld, and their normal littersmates, WBB6F1+/+(+/+) or WCB6F1-+/+, respectively, were used in initial studies. Each mouse strain has a separate genetic defect in the ability to generate mast cells, but a similar phenotype (i.e., mast cell deficiency, Galli and Kitamura, 1987). The mice were purchased from the Jackson Laboratory (Bar Harbor, ME) and housed in the USC vivarium. Food and water were available *ad libitum* and the mice were housed on a 12:12 h light:dark cycle. The mast cell-deficient mouse strain leading to mast cell deficiency allows reconstitution of the mice with bone marrow-derived mast cells (BMMC) from wild-type mice (Kitamura *et al.*, 1978).

**Preparation of bone marrow-derived mast cells.** Bone marrow cells were obtained from femurs of 10-week-old WBB6F1-+/+(+/+) mice. WBB6F1-W/W (W/W) mice were reconstituted with purified cultured BMMC from wild-type mice at age 90 days or more (Ramos *et al.*, 1991, 1992). BMMC were prepared according to a procedure previously described (Razin *et al.*, 1981; Frandji *et al.*, 1993). Briefly, 5 x 10⁶ bone marrow cells were suspended in 25 ml enriched culture medium: RPMI 1640 supplemented with 10% heat-inactivated fetal calf serum (FCS), antibiotics (100 μg/ml streptomycin, 100 U/ml penicillin, 250 μg/ml amphotericin B), 25 mM Hepes, 4 mM L-glutamine, 0.1 mM nonessential amino acid, 1 mM sodium pyruvate, and 50% WEHI-3-conditioned medium (WEHI-3-CM, source of IL-3) in 75-cm² tissue culture flasks (Falcon) and incubated at 37°C in humidified 5% CO₂/95% air. The cell suspensions were centrifuged at 400 g for 10 min and the cells were resuspended in fresh medium at 7-day intervals. Macrophages present within the cultures were removed by attachment to plastic surfaces of a flask. A sample of the nonadherent cells was stained with toluidine blue (pH 3.5) to determine the percentage of metachromatic cells (Frandji *et al.*, 1993).

WEHI-3-CM was produced by seeding WEHI-3 cells (1 x 10⁶ cells/ml) into culture medium [Iscove’s modified Dulbecco’s medium with 0.05 mM 2-mercaptoethanol, 4 mM L-glutamine, and 10% FCS] and incubating these cultures at 37°C in 5% CO₂/95% air for 3 days. The cells were then transferred into medium without serum for an additional 3 days. This serum-free medium was utilized as WEHI-CM above. The supernatant was centrifuged at 600 g for 20 minutes, filtered through a 0.2-μm filter system, and stored at -70°C until use. All reagents were purchased from GBICO (Grand Island, NY).

**Mast cell reconstitution.** After a 3-week culture with medium supplemented with WEHI-CM, the cultures of bone marrow cells contained almost exclusively mast cells (BMMC). An aliquot, 5 - 10 x 10⁶, of BMMC was injected intraperitoneally into each mouse undergoing reconstitution. The mast cell-deficient mice reconstituted with cultured BMMC were utilized 3 weeks after injection (appropriately 16 to 17 weeks of age). The ability to reconstitute with BMMC was assessed through microscopic examination for the presence of mast cells in the peritoneal lavage fluid from each mouse stained with Alcian blue. In addition, a portion of the skin from one control mouse in each study was fixed in Carnoy’s solution, stained with toluidine blue, and examined microscopically for the presence of mast cells. Different groups examined in these studies were designated as follows: (1) W/W + corn oil; (2) W/W + malathion (600 mg/kg same as below); (3) W/W + BMMC + corn oil; (4) W/W + BMMC + malathion; (5) +/+ + corn oil; (6) +/+ + malathion.

**Macrophage Functional Assays**

**Macrophage respiratory burst function.** The respiratory burst function was assessed by the measurement of hydrogen peroxide production after stimulation with phorbol ester as previously described (Rodgers and Ellefson, 1992; Rodgers, 1995). Briefly, marine peritoneal cells were harvested, the viability was assessed by trypan blue exclusion, and the cells were resuspended at 2 x 10⁶ cells/ml in phosphate-buffered saline (PBS, pH 7.4). Aliquots, 100 μl, of cell suspension were added into wells of a 96-well microtiter plate (Falcon). After a 1-hr incubation, cells were washed three times to remove nonadherent cells. Ninety microliters of PBS with 2,7-dichlorofluorescein dichloroacetaie (DeDF) (5 μM final concentration; Kodak Chemicals, Rochester, NY) was added into each well and incubated for 15 min. Ten microliters of PMA (100 ng/ml, Sigma, St. Louis, MO) was added into each well to stimulate hydrogen peroxide production. The increase in fluorescent product was measured after a 1-hr incubation at 37°C on a Millipore fluorescence measurement system (Cytofluor 2350) [excitation, 485 nm; emission, 530 nm]. The intensity of the fluorescent product, 2,7-dichlorofluorescein, was compared to a standard (Polysciences, Warrington, PA).

**Phagocytosis assay.** Assessment of the phagocytic capacity of peritoneal macrophages was conducted as previously described (Rodgers et al., 1985; Rodquis and Ellefson, 1988). Yeast particles (Sigma) were hydrated in PBS and boiled for 1 hr to inactivate the particles. The inactivated particles were then opsonized by mixing 2 x 10⁶ yeast particles/ml with heat-inactivated serum from WBB6F1-+/+ mice. After 1 hr, the particles were washed three times with PBS to remove excess serum proteins. In order to adhere the peritoneal cells for the measurement of phagocytic capacity, 2 x 10⁶ mononuclear cells in 1 ml were placed onto a glass coverslip (22 x 22 mm) that had been placed in a 35-mm tissue culture dish. The cells were then allowed to adhere in a humidified environment of 5% CO₂ in air at 37°C for 1 to 2 hr. At the end of this incubation, the coverslip was washed gently six times with PBS to remove nonadherent cells. After each rinse, one end of the coverslip was blotted with an absorbent towel to remove the loosely associated liquid. An aliquot, 100 μl, of opsonized yeast was then added to the adherent peritoneal cells and incubated for 20 min longer. The coverslips were then washed three times to six times and placed cell side down on the microscope slide for assessment. The number of yeast ingested per macrophage was determined for 100 to 200 cells per coverslip.

**Humoral Immune Response**

**Immunization and sera collection.** The mice were immunized to sheep red blood cells (SRBC, Colorado Serum, Denver, CO), 2 x 10⁶ SRBC/mouse, via intraperitoneal injection. At Days 3, 5, and 7 after immunization, blood was harvested from the retroorbital space (Days 3 and 5) under Metofane anesthesia or by cardiac puncture immediately after termination on Day 7. The blood was allowed to clot overnight at 4°C and centrifuged for 15 min at 800g, and the serum harvested to assay for antibodies to SRBC. The sera were stored in cryogenic vials at -20°C until assayed.
ELISA plates. The ELISA plates were made 1 to 3 days prior to performing the assay. Fifty microliters of 0.1 mg/ml poly-L-lysine (Sigma) were added to each well of a U-bottom microtiter plate for ELISA (Dynatech, Chantilly, VA) and incubated for 30 min at room temperature. The plates were then washed three times with distilled water. Plasma membrane preparations were generated by lysis of washed SRBC in distilled water followed by sonication for 1 min and centrifuged at 10,000g for 10 min. The pellet from this centrifugation step was then diluted into coating buffer (carbonate buffer, pH 9.6) at an equivalent of 1 x 10⁶ cells/ml. Fifty microliters of this SRBC plasma membrane preparation was added to each well followed by 25 μl/well of 1.5% glutaraldehyde. The plates were then covered with film wrap and incubated for 1 hr at room temperature. The plates were then covered with film wrap and the remaining binding sites were blocked with 100 μl/well PBS, pH 7.2, with 0.5% bovine serum albumin, 0.01% Tween, and 0.01% sodium azide (blocking buffer). The plates were then covered with film wrap and incubated for either 1 hr at 37°C or 2 hr at room temperature. The plates were then washed three times with PBS containing 0.01% Tween (PBS–Tween) and two times with distilled water. The plates were stored at 4°C until use.

ELISA assay. The sera were diluted 1:200, 1:400, and 1:800 in diluting buffer (PBS, pH 7.2, containing 0.2% BSA). Each diluted serum sample was aliquoted in triplicate on two plates (one to measure anti-SRBC IgG levels and the other to measure anti-SRBC IgM levels) at 50 μl per well. The plates were incubated at 37°C for 2 to 3 hr. After this incubation, the plates were washed three times with PBS–Tween. Second antibody (rabbit anti-mouse IgG or IgM, as appropriate, coupled with horseradish peroxidase, Sigma), diluted 1:500 in diluting buffer, was then added into each well. These plates were then incubated for 1 hr at room temperature and the plates were washed five times with PBS–Tween and three times with distilled water. Thereafter, 100 μl substrate, 2,2’-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS; 0.5 mg/ml in citrate phosphate buffer, pH 4.0, Sigma) with 0.015% hydrogen peroxide (Sigma), was then added to each well. After 30 min of incubation at room temperature, the reaction was stopped by addition of 25 μl 0.33 M sodium fluoride. The absorbance of each well was then measured on a Dynatech Microplate Reader MR650 with a Apple IIC computer attached.

RESULTS

Macrophage Functional Assays

Initial studies were done on mice that were 6–8 weeks old to determine if the wild-type mice from two separate strains that have mast cell-deficient counterparts (with defects in two separate sites for mast cell differentiation) had an increase in their macrophage function following acute, oral administration of malathion. In addition, the effects of oral administration of malathion on the macrophage function of these two strains of mast cell-deficient mice were determined. The results from these studies are shown in Table 1. As can be seen, in both strains of mice, acute, oral administration of 300 mg/kg malathion to the wild-type mice elevated the production of hydrogen peroxide by peritoneal leukocytes while the same treatment suppressed the production of hydrogen peroxide by the peritoneal leukocytes of mice genetically altered to be deficient in mast cells (W/W+ and Sl/Sld). Because both strains were responsive to malathion treatment and the genetic defect that leads to the phenotype of mast cell deficiency in the W/W+ mice allowed reconstitution of mast cells by injection with bone marrow-derived mast cells (BMMC) from the wild-type mice, all further studies were conducted using W/W+ mice.

In order to reconstitute the mice, older mice were used (90 days at the time of injection of BMMC). Attempts to reconstitute younger mice (6–8 weeks at the time of injection) were not successful (data not shown). Because the mice were used for the experiments 20–21 days after injection, the mice used in these studies were 16–17 weeks of age at treatment rather than 6–8 weeks of age as above. The wild-type and mast cell-deficient controls were age matched to the reconstituted group. In this study, acute, oral administration of 600 mg/kg malathion did not suppress macrophage function in the mast cell-deficient mice, but did enhance the function of peritoneal macrophages in the wild-type and the mast cell-deficient mice that had been reconstituted with BMMC (Fig. 1 and Tables 2 and 3). In Fig. 1, the effects of malathion administration on the respiratory burst of peritoneal macrophages after stimulation in vitro with phorbol ester are shown. As stated above, malathion did not affect the ability of macrophages from mast cell-deficient mice to generate hydrogen peroxide, but did enhance the respiratory burst function of wild-type and reconstituted mice. This same pattern of results was observed with regard to the effects of malathion on the phagocytosis of opsonized yeast by peritoneal macrophages (Table 2 [percentage of macrophages with no yeast ingested] and Table 3 [average number of yeast ingested per macrophage]). However, the phagocytic capability of the reconstituted mice was reduced compared to wild-type controls (Table 3).

Humoral Immunity

Initial studies were conducted with mast cell-deficient mice to determine if the ability of the mice to respond to
FIG. 1. The effects of malathion on the production of hydrogen peroxide are shown. The groups are as follows: (1) W/W + corn oil; (2) W/W + 600 mg/kg malathion; (3) W/W + BMMC + corn oil; (4) W/W + BMMC + 600 mg/kg malathion; (5) wild-type mice + corn oil; and (6) wild-type mice + 600 mg/kg malathion. Twenty-four hours after treatment, peritoneal macrophages were harvested for assessment for hydrogen peroxide production. Groups 4 and 6 are increased compared to groups 3 and 5 (p < 0.05). These data are the mean and standard deviation of data from 9 mice (3 mice per experiment, 3 experiments).

antigenic challenge in the generation of a humoral immune response and the concentration of antigen necessary for an optimal response were modified due to the absence of mast

<table>
<thead>
<tr>
<th>Table 2</th>
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<tr>
<td>Effect of Malathion Administration on Phagocytosis by Macrophages</td>
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<table>
<thead>
<tr>
<th>Groups</th>
<th>Percentage of macrophage with no yeast (mean ± SEM)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wt + corn oil</td>
<td>84.00 ± 2.65</td>
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</tr>
<tr>
<td>Wt + malathion</td>
<td>66.67 ± 4.84</td>
<td>0.035</td>
</tr>
<tr>
<td>W/W + BMMC + corn oil</td>
<td>92.33 ± 3.67</td>
<td>0.035</td>
</tr>
<tr>
<td>W/W + BMMC + malathion</td>
<td>77.33 ± 3.48</td>
<td>0.041</td>
</tr>
<tr>
<td>W/W + corn oil</td>
<td>91.00 ± 2.00</td>
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</tr>
<tr>
<td>W/W + malathion</td>
<td>92.33 ± 3.18</td>
<td>0.741</td>
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</table>

Note. The effect of oral administration of malathion on macrophage phagocytosis was examined. Mast cell-deficient WBB6F1-W/W (W/W) mice, mast cell-reconstituted WBB6F1-W/W (W/W + BMMC) mice, and wild-type WBB6F1-+/+ (Wt) mice were treated with corn oil or malathion (600 mg/kg) via oral gavage and the phagocytic capability was determined 24 hr later. These data represent the mean number of yeast ingested per macrophage after examination of 100 to 200 adherent cells per animal. Each data point is the mean and standard error of nine mice in three experiments. The p values are from Student’s t tests analysis of the data with the treated group compared with equivalent control.

Cells. A range of antigen concentrations (0.4 – 10 \times 10^6 SRBC injected intraperitoneally) were tested. The mast cell-deficient mice gave a vigorous immune response to SRBC injection at all antigen concentrations that was, in fact, superior to that of the wild-type mice (data not shown).

Studies were then conducted to determine the effects of oral administration of malathion on the generation of a primary immune response to SRBC. These studies were only conducted in the older mice that were a part of the reconstitution studies. As can be seen in Table 4, acute administration of malathion to wild-type or mast cell-deficient mice reconstituted with BMMC from wild-type mice increased the level of IgM antibody to SRBC on Days 3 and 5 after immunization. On the other hand, the level of serum IgG antibody generated was not increased by malathion administration in these mice. In mast cell-deficient mice, however, administration of malathion reduced the level of serum IgM and IgG antibodies to SRBC on Days 3 and 5 after immunization. On Day 7 after immunization, malathion increased the level of serum IgM antibody to SRBC in mast cell-deficient mice.

**DISCUSSION**

Malathion is a widely used organophosphate pesticide used in situations where the public would be exposed (Weeks et al., 1977). Studies have shown that administration of non-cholinergic doses of malathion elevated the generation of a primary humoral immune response and macrophage functions (Rodgers et al., 1986; Rodgers and Ellefson, 1990, 1992). In addition, in vivo administration of malathion led to
determine if the presence of mast cells was required for theory mediators by and other activities of mononuclear cells cited that mast cell products and more specifically heparin (Yoffee et al., 1993; Schultz et al., and other polyanions increased the production of inflamm-
Okamato 1990). Studies by Yoffee and others indi-
tion (Dileepan 1990, 1993).
These data are from one experiment and other experiments gave comparable results.
other polyanions increased the production of inflammatory factors, which include cytokines, lipid-derived mediators, histamine, heparin, proteases, and other enzymes, chemotactic factors, and proteoglycans, can modulate macrophage function and show that macrophages can ingest mast cell granules (perhaps through a specific receptor on the macrophage mem-
brane) after degranulation (Bonavida et al., 1990; Klein et al., 1989; Baggiolini et al., 1982; Lindahl et al., 1979; Ishi-
zaka and Ishizaka, 1984; Schwartz and Austen, 1984; Hen-
derson and Kaliner, 1978; Dileepan et al., 1989). Other studies have shown that mast cell granules inhibit macrophage tumoricidal activity (perhaps through inhibition of binding of lipopolysaccharide to its receptor) and nitric oxide production (Dileepan et al., 1990, 1993).

Macrophages have also been shown to express receptors for mast cell mediators, including histamine and heparin (Bleiberg et al., 1983; Feder et al., 1991; Gespach et al., 1991). Through activation of these receptors, alterations in macrophage activity have been observed. For example, histamine was shown to increase intracellular calcium in and interleukin 1 production by macrophages (Ohno et al., 1991; Okamato et al., 1990). Studies by Yoffee and others indicated that mast cell products and more specifically heparin and other polyanions increased the production of inflammatory mediators by and other activities of mononuclear cells (Yoffee et al., 1985; Bleiberg et al., 1993; Schultz et al., 1977; Jaques, 1979). Therefore, studies were conducted to determine if the presence of mast cells was required for the expression of the alterations in immune effects observed after administration of noncholinergic doses of malathion.

In this report, it was shown that acute, oral administration of noncholinergic doses of malathion to mast cell-deficient mice suppressed (young mice) or did not affect (older mice) the function of peritoneal macrophages as measured by the production of hydrogen peroxide and phagocytosis of opsonized yeast. In addition, administration of malathion to mast cell-deficient mice (older) suppressed the level of serum IgM and IgG antibodies to SRBC on Days 3 and 5 after immunization and increased the level of serum IgM antibodies to SRBC on Day 7 after immunization. These data show that in the absence of mast cells oral administration of malathion can suppress macrophage and humoral immune function.

On the other hand, reconstitution of the mast cell population of these mice with BMMC from wild-type mice restored the ability of oral exposure to malathion to increase macrophage function (as measured by the generation of a primary immune response to a T-dependent antigen) in a manner comparable to wild-type mice. These data indicate that the genetic defect in the mast cell-deficient mice that led to this phenotype did not alter the ability of the mice to respond to malathion. Therefore, these studies support the hypothesis that mast cells are involved in the enhanced macrophage and humoral immune function observed after administration of malathion.

As stated, mast cells were shown to have a role in the

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**Table 4**

<table>
<thead>
<tr>
<th>Group</th>
<th>Optical density, 410 nm, mean ± SD postimmunization</th>
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<tbody>
<tr>
<td></td>
<td>Day 3</td>
</tr>
<tr>
<td><strong>IgM</strong></td>
<td></td>
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<tr>
<td>Wt + corn oil</td>
<td>0.324 ± 0.030</td>
</tr>
<tr>
<td>Wt + malathion</td>
<td>0.400 ± 0.038*</td>
</tr>
<tr>
<td>W/W’ + BMMC + corn oil</td>
<td>0.375 ± 0.038</td>
</tr>
<tr>
<td>W/W’ + BMMC + malathion</td>
<td>0.514 ± 0.051*</td>
</tr>
<tr>
<td>W/W’ + corn oil</td>
<td>0.551 ± 0.056</td>
</tr>
<tr>
<td>W/W’ + malathion</td>
<td>0.235 ± 0.019*</td>
</tr>
<tr>
<td><strong>IgG</strong></td>
<td></td>
</tr>
<tr>
<td>Wt + corn oil</td>
<td>0.320 ± 0.040</td>
</tr>
<tr>
<td>Wt + malathion</td>
<td>0.391 ± 0.043</td>
</tr>
<tr>
<td>W/W’ + BMMC + corn oil</td>
<td>0.318 ± 0.037</td>
</tr>
<tr>
<td>W/W’ + BMMC + malathion</td>
<td>0.400 ± 0.032*</td>
</tr>
<tr>
<td>W/W’ + corn oil</td>
<td>0.347 ± 0.032</td>
</tr>
<tr>
<td>W/W’ + malathion</td>
<td>0.241 ± 0.021*</td>
</tr>
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</table>

* *p* value =< 0.05 comparing corn oil and malathion group.

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Note. Wild-type WBB6F1+/+ (Wt), mast cell-deficient WBB6F1- W/Wv (W/W’), and reconstituted W/W’ (W/W’ + BMMC) mice were treated with corn oil or 600 mg/kg malathion via oral gavage. The mice were immunized with SRBC and serum was harvested at various postimmunization days. The level of antibodies in the serum was assessed via ELISA. Experiments were performed three times with three mice per group in each experiment. These data are from one experiment and other experiments gave comparable results.

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increase in macrophage and humoral immune function observed after oral administration of malathion. These data, together with previous studies of the kinetics of macrophage activation after malathion administration, are consistent with the hypothesis that mast cells rapidly interact with macrophages to modulate a variety of functional parameters including the generation of oxygen radicals and Fc receptor-mediated phagocytosis. Recent studies from one laboratory has provided compelling evidence that mast cell granules increased the production of hydrogen peroxide by alveolar macrophage through an increase in the conversion of superoxide anion to hydrogen peroxide. This was shown to be due to the fact that superoxide dismutase was a component of the mast cell granules and addition of this exogenous enzyme to the macrophages by ingestion of the granules increased hydrogen peroxide production (Dileepan et al., 1989; Dileepan and Stechschulte, 1986; Rock et al., 1990; Henderson and Kaliner, 1978). This may be one mechanism by which oral administration of malathion increased the production of hydrogen peroxide. On the other hand, studies by Rock et al. (1990) showed that mast cell granules also contain peroxidase, an enzyme which metabolizes hydrogen peroxide to water, that can actually decrease the amount of hydrogen peroxide measured. Therefore, the results contained in this paper may be the result of (1) actual increases in the respiratory burst system per se or (2) the addition of exogenous enzymes to the system by the granules.

Studies have also shown that mast cells can respond to inducer T lymphocytes and that activated mast cells express Class II major histocompatibility antigens. Based upon these studies, some have suggested that mast cells may act as antigen-presenting cells (Warbrick et al., 1995; Frandji et al., 1993; Nabel et al., 1981). In this study, the presence of mast cells was necessary for the observed increase in the generation of a primary humoral immune response after acute administration of malathion. It is therefore possible that the increase in this immune parameter is the result of alterations in both macrophage and mast cell function after malathion exposure.

The data also showed that as the mast cell-deficient mice aged, oral administration of malathion no longer altered macrophage function. In contrast, the effect of malathion on the macrophage function of wild-type mice was not altered as the mice aged (6–8 weeks versus 16–17 weeks). There is no explanation for these differences at this time. However, the humoral immune response was inhibited in mice in which macrophage function was not altered; therefore, in the absence of mast cells, the suppression in antibody formation is not always the result of alterations in macrophage function.

In summary, these data suggest that the presence of mast cells is necessary for the observed increases in macrophage function and humoral immune responses after malathion exposure. The mechanism by which malathion caused mast cell degranulation and the mediator that is released by the mast cell to affect these functional parameters are currently unknown. There are several mast cell mediators that are capable of stimulating macrophage and humoral immune functions. Determination of the mediator involved is the subject of ongoing studies.

REFERENCES


