Difference in the Susceptibility to *Brugia pahangi* Infection between Male and Female BALB/c Mice: Differences of Effector Cell Responses between Sex

Hirokuni NAKANISHI

Department of Medical Zoology, Nagasaki University School of Medicine, 12−4 Sakamoto−machi, Nagasaki 852, Japan

Abstract: Difference in the susceptibility to *Brugia pahangi* infection between male and female BALB/c mice was examined. In a primary infection, male mice showed greater susceptibility than did females as defined by counting the number of worms recovered from the peritoneal cavity. Sex difference appeared at the early phase of primary infection (5−10 days) and continued for at least 7 weeks of infection. Inoculation with the 3-rd stage larvae was effective in inducing sex difference, whereas inoculation with the 4-th stage larvae had no effect. Therefore, sex difference in susceptibility seems to be induced by the 3rd stage larvae (possibly molting stage larvae). Since sex difference was only observed in a primary infection but not in a challenge infection, the expression of sex difference might be dependent upon some differences of development of early phase of immune response to the larval worm of *B. pahangi* between the sex. Thus, in the present study, the difference in immunological response of host to filarial worm was examined. Significantly great number of effector cell infiltrations (macrophages and eosinophils were predominant) were observed in the peritoneal cavities of female mice 10 days after infection. Whereas no significant difference in the levels of anti−*B. pahangi* IgG, IgM and IgE were observed at this time of infection, the cellular reaction that occured in female mice 10 days postinfection may be one of the factors which reflects the differential sex susceptibility of host in *B. pahangi*−mouse model.

Key words: sex difference, susceptibility, *Brugia pahangi*, BALB/c mouse, effector cells

INTRODUCTION

It is a common knowledge that male hosts show higher susceptibility to certain species of parasites than do female hosts (Solomon, 1969; Goble and Konopka, 1973). The sex difference in susceptibility of the host to filarial worm is frequently reported in the epidemiological studies on filarial infection (Jakowski *et al.* cited in Ash, 1971; Beye and Gurian, 1960; Dondero and Menon, 1972; Murray, 1948; Nagatomo, 1960; Napier, 1944;

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Nelson *et al.*, 1962; Omori *et al.*, 1962; Rosen, 1955; Sasa *et al.*, 1970) and in experimental filariasis by using the rodents model (Ash and Riley, 1970; Ash, 1971; 1973; Sucharit and MacDonald, 1972). Although some possible explanation are given to differential sex susceptibility, Wesley (1973) concluded that androgen is one of the factors which regulate the susceptibility of the jird to *Brugia pahangi* infection.

Recently Abe *et al.* (1985) reported that differential sex susceptibility of mouse to *Strongyloides ratti* is due to the difference in strength of host defence mechanism at a given stage of infection. Their studies encourage to examine whether preferential susceptibility of the male host to filarial worms depends on the difference in host immune response at any specified stage of infection.

So far the jird−*B. pahangi* model has been commonly used for the experimental rodent filariasis, because it is easy to handle model, however, is less useful for the immunological studies, because the inbred jirds are not commercially available. Recently BALB/c mice were reported to show less susceptibility, but allow some larvae to develope to the adult worm, when the intraperitoneal route of infection is used (Mackenzie *et al.*, 1985). The BALB/c mice, therefore, were used in the present study as the experimental animal host.

Materials and Methods

Animals

Inbred male and female BALB/c mice were raised in our laboratory. The parental stocks were kindly given by Dr. S. Matsuo, Institute of Tropical Medicine, Nagasaki University. Mice, over 12 weeks old, were used in all the experiments.

Preparation of antigen

B. pahangi adult worms, obtained from peritoneal cavities of jirds which have been intraperitoneally inoculated with 300−400 infective 3rd stage larvae (L3) 9−10 weeks previously, were washed extensively in phosphate−buffered saline (PBS, pH 7.2). Worms were homogenized in a glass homogenizer and extracted in PBS by continuous stirring overnight at 4 C. The extract was centrifuged at 12,000 r.p.m. for 1 hr. After centrifugation, the protein concentration of the supernatant was measured by the method of Lowry *et al.* (1951).

Preparation of sera

Male and female BALB/c mice intraperitoneally inoculated with 50 *B. pahangi* L3 were bled on day 0, 5, 10 and 15 of infection.

Inoculation of parasites

Infective stage larvae of *B. pahangi* were obtained from mosquitoes (*Aedes aegypti*) which had been fed on microfilaremic Wistar rats 2 weeks previously. Mice were inoculated intraperitoneally with 50 L3 suspended in 0.5ml of Hanks' balanced salt solution (HBSS).

The 4th stage larvae (L4) were obtained from BALB/c mice which had been inoculated intraperitoneally with 400−500 L3 of *B. pahangi* 20 days previously. Mice were inoculated with 40 L4 in 0.5ml of HBSS through a 18−gauge needle into the peritoneal cavity.

Immunization and challenge infection

BALB/c mice, 7 to 8 weeks old, were immunized by a subcutaneous injection of 100 naive *B. pahangi* L3 in the left groin. Five weeks later, immunized mice were challenged intraperitoneally with 50 homologous L3.

Recovery of worms from peritoneal cavity

The peritoneal cavity was examined for recovery of worms at various time points postinoculation (PI). To avoid coagulation of peritoneal cells, 0.5ml of heparinized HBSS (4 u/ml) was injected into peritoneal cavity of each animal. Then, they were killed by ether, the peritoneal cavity was flushed with 4.5ml of HBSS. Worms were collected in a petri dish and counted immediately with a stereo microscope at 6 x magnification. Then the mouse was soaked in HBSS in a 50ml tube for 2 hours, after that live worms at the bottom of the tube were collected and counted under a stereo microscope. The summation of live worm counts from a petri dish and a bottom of the tube was expressed as the total number of recovered worms for each mouse.

Differential count of peritoneal exudate cells

Peritoneal exudate cells (PEC) were collected from peritoneal cavities of male and female mice by washing with 5ml of heparinized HBSS. Total number of PEC was determined using an improved Neubauer's hemocytometer. Differential count was made by counting 200 cells in a smear stained with Giemsa.

Passive cutaneous anaphylaxis (PCA) reaction

PCA reaction was carried out according to the method of Ovary *et al.* (1975) with a slight modification. Test sera were serially diluted with PBS and injected intradermally into normal indicator rats in 0.05ml volume. Four hours later, these rats received 1mg of *B. pahangi* antigen intravenously together with 1ml of a 1% Evans blue solution. Thirty minutes later, the animals were sacrificed and their skin was reversed to determine the bluing reactions. Bluings more than 5mm in diameter were considered as a PCA positive.

Enzyme−linked immunosorbent assay (ELISA)

ELISA for detecting specific IgG or IgM levels of *B. pahangi* antigen were carried out according to the method of Tanaka *et al.* (1983) using crude *B. pahangi* adult worm antigen (2.5 μg/ml). Peroxidase-conjugated rabbit anti−mouse IgG and IgM were commercially obtained.

Statistical analysis

Statistical significance of differences in mean values was assessed using Student's t−test or Welch's t−test. Statistical significance was determined using $P=0.05$ criterion.

RESULTS

Susceptibility to a primary infection

Adult male and female mice (more than 12 weeks old) were injected intraperitoneally with 50 L3. At 7 weeks PI, some live worms were recovered from the peritoneal cavity. And there was considerable difference in the number of worms recovered from male and female mice (Fig. 1). This preliminary experiment showed that male mice were more susceptible to *B. pahangi* infection than females ($P<0.01$). To know the time when sex difference became apparent, adult male and female mice were injected intraperitoneally with 50 L3 and their peritoneal cavities were subsequently examined at a given interval. No significant difference was observed on day 5 PI (Fig. 2). Significant difference in

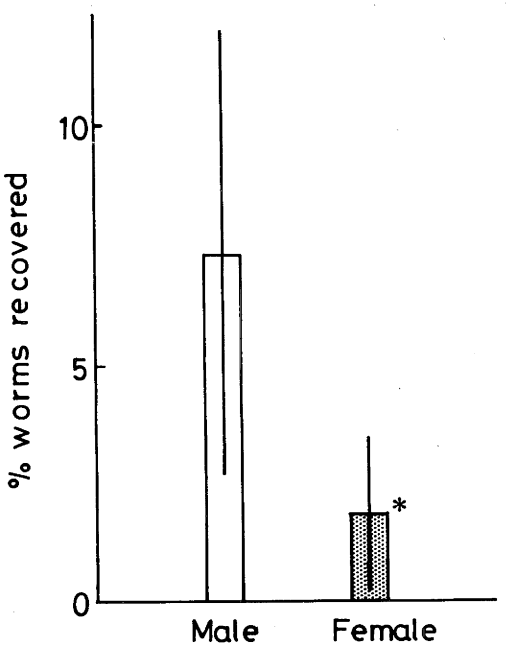

Fig. 1. Recovery rates of worms from the peritoneal cavities of male (open bar) and female (dotted bar) BALB/c mice at 7 weeks after a primary infection with *B. pahangi* L3. Ten male mice and eleven females were inoculated intraperitoneally with 50 *B. pahangi* L3 and the live worms were collected from their peritoneal cavities at 7 weeks postinoculation. Vertical bar indicates the standard deviation of the mean. *Recovery rate of worms from female mice was significantly less than that from males ($P<0.01$).

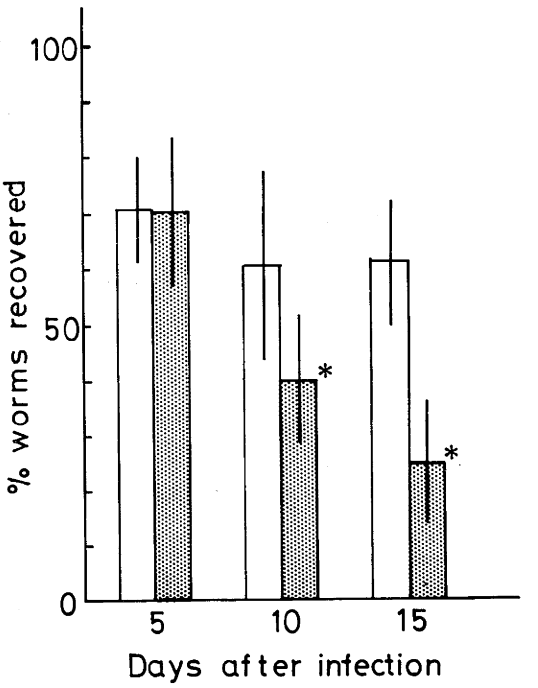

Fig. 2. Recovery rates of worms from the peritoneal cavities of male (open bars) and female (dotted bars) BALB/c mice at various times after an intraperitoneal inoculation of 50 L3. From left to right each bar represents the mean from eleven, ten, eleven, eleven, ten and seven mice, respectively. Vertical bars indicate the standard deviation of the mean. *As shown in Fig. 1 (10 days PI, $P<0.005$; 15 days PI, $P<0.001$).

the susceptibility between sex to *B. pahangi* infection was observed on day 10 and 15 PI ($P<0.005$ and $P<0.001$, respectively). The percent of worms recovered from male mice on day 10 and day 15 PI were as high as those on day 5 PI. However, those from females were significantly reduced on days 10 and 15 PI.

Difference in survival of L3 and L4 in peritoneal cavities of male and female mice

To clarify which stage of worms to be important for the target that induces host sex difference in the susceptibility to *B. pahangi* infection, L3 and L4 were inoculated into the peritoneal cavities of male or female mice. As shown in Fig. 3, statistically significant ($P<0.001$) sex difference (the female mice showed less susceptibility than the males) was observed only when L3 were inoculated into mice. The recovery rate of L4 was rather higher in female mice than that in male mice, but it was not statistically significant.

Serological data

Kinetics of specific serum IgG and IgM antibody levels of *B. pahangi* was examined by using ELISA. As shown in Table 1, both classes of antibody levels increased gradually but remained low during the observation period of 15 days PI and no difference in levels of these antibodies between sex were observed except IgM which

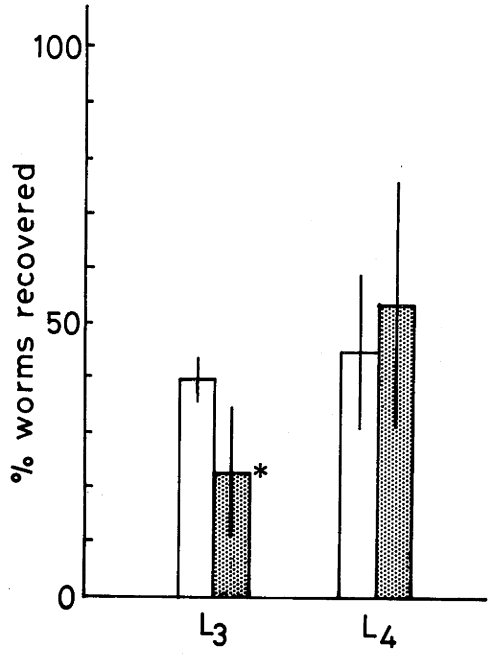

Fig. 3. Recovery rates of worms at 15 days after inoculation of 50 L3 and 40 L4 from male (open bars) and female (dotted bars) mice. From left to right each bar represents the mean from seven, seven, five and five mice, respectively. Vertical bars indicate the standard deviation of the mean. *As shown in Fig. 1 ($P<0.001$).

Table 1. Anti−*B. pahangi* antibodies in male and female mice infected intraperitoneally with 50 L3 of *B. pahangi*

Days postinfection	IgG		IgM	
	Male	Female	Male	Female
0	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000
5	0.080±0.072	0.149±0.051	0.000±0.000	0.042±0.079
10	0.212±0.117	0.224±0.129	0.082±0.093	0.108±0.062
15	0.195±0.137	0.162±0.093	0.062±0.093	0.223±0.097*

Values are the mean absorbance (experimental − control) at 490nm and standard deviation from five mice. Antibodies to crude *B. pahangi* adult worm antigen were measured using an ELISA.

*Significantly higher than males ($P<0.05$).

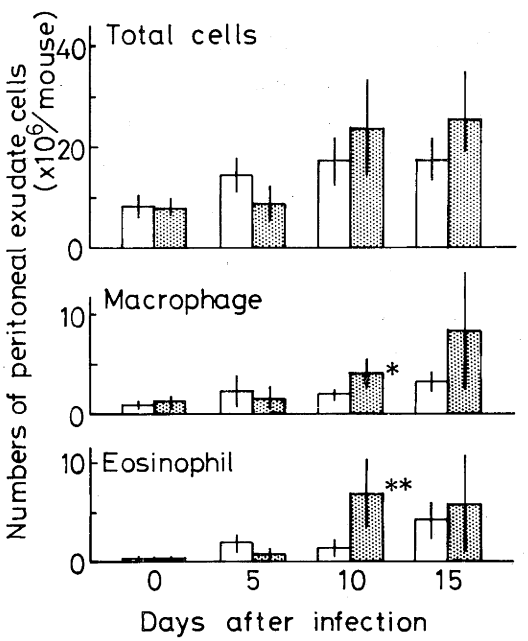

Fig. 4. Total and differential counts of peritoneal exudate cells at 0, 5, 10 and 15 days after inoculation of 50 L3 of *B. pahangi*. Open bars and dotted bars indicate males and females, respectively. From left to right each bar represents the mean from three, four, four, five, five, six, four and four mice, respectively. Vertical bars indicate the standard deviation of the mean. *$P<0.05$, **$P<0.01$.

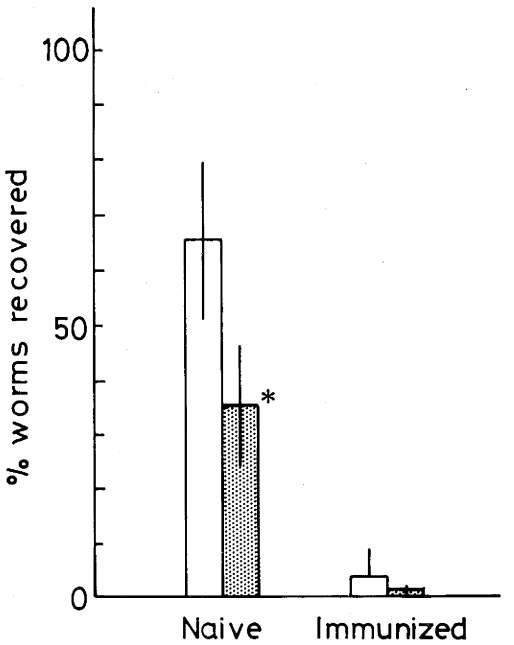

Fig. 5. Comparison of the recovery rates of worms from the peritoneal cavities at 15 days postinoculation between naive male (open bar) and female (dotted bar) mice and immunized male (open bar) and female (dotted bar) mice. Immunization was done by a subcutaneous injection with 100 L3 five weeks previously. From left to right each bar represents the mean from seven, seven, six and ten mice, respectively. Vertical bars indicate the standard deviation of the mean. *As shown in Fig. 1 ($P<0.001$).

was higher in females than in males at 15 days PI. Specific IgE antibody against *B. pahangi* worm antigen was measured by PCA reaction. No significant level of IgE antibody was detected during 15 days of observation.

Cytological data

The responsiveness of peritoneal cells against *B. pahangi* larvae was examined (Fig. 4). However, no difference in the total number of PEC and differential counts of macrophages and eosinophils between sex was observed until 5 days PI. On days 10 and 15 PI, total PEC, macrophages and eosinophils showed a tendency to increase in number in females rather than in males. Statistically significant increase in numbers were observed especially in macrophages and eosinophils on day 10 PI ($P<0.05$, $P<0.01$, respectively).

Susceptibility to a challenge infection

As shown in Fig. 5, the recovery rate of worms in the challenge infection was significantly lower than that in the primary infection ($P<0.001$). No significant difference in the recovery rate of worms was observed between male and female mice in the challenge infection.

Discussion

The present paper clearly discribed that BALB/c mice show differential sex susceptibility to *B. pahangi* infection. Adult male BALB/c mice showed higher susceptibility than female animals as defined by percent recovery of worms from the peritoneal cavity. This difference became significant at very early phase of infection (10 days PI), and remained unchanged for 7 weeks PI, the time when worms developed into young adult stage in mice (Sakamoto *et al.*, 1982). Sex difference seems to appear around the time of the 3rd molt, because the molt from the 3rd to the 4th stage occurs at about 7−10 days after infection in the mouse−*Brugia* system (Sakamoto *et al.*, 1982). Then, the experiment was designed to investigate which stage of larvae (3rd or 4th stage larvae) can induce this difference between sex. Sex difference (expressed as a higher susceptibility in males than in females) was observed only when the 3rd stage larvae were inoculated. When the 4th stage larvae were inoculated, there were not significant difference of recovery rates between sex, though slightly less recovery rates were observed in males than in females. These results suggest that difference in the susceptibility to a primary *B. pahangi* infection between sex was induced by the 3rd stage larvae and/or the molting stage larvae.

In general, the causes of the failure of the parasite to mature in the undefinitive host were complicated. Mouse has been considered to be an undefinitive host to lymphatic dwelling filarial worm. However, in the mouse−*Brugia* system, an immune response, rather than some innate physiological or biochemical insufficiency, played an

important role in the failure of *B. pahangi* to develope in normal mice, since the successful development of the same parasite was seen in athymic (nude) mice (Vincent *et al.*, 1982) and T−cell−deprived mice (Suswillo *et al.*, 1981). So present paper examined whether host immune response to filarial infection differs between male and female BALB/c mice.

So far antibody−dependent cell adherence to parasite and their cytotoxic activity against worms have been identified as one of the major effector mechanisms to parasite worms (Butterworth *et al.*, 1977; Mackenzie *et al.*, 1977; Perrudet−Badoux *et al.*, 1978; Weiss and Tanner, 1979; Butterworth, 1984). Thus, serum levels of antibodies and effector cells infiltrated in the peritoneal cavities of mice during the early phase of infection (15 days PI) were examined. The present results did not show any difference of antibody (IgG and IgM) levels between sex except only one data of IgM obtained on day 15 PI. And increased level of IgE was not detected in both sex of mice. In contrast to humoral immune response, the number of peritoneal exudate cells was likely to increase in female mice than in males 10 days PI, and the number of macrophages and eosinophils ($P<0.05$, $P<0.01$, respectively) significantly increased in the peritoneal cavities of female mice (Fig. 4). The time of appearance of differential response in macrophages and eosinophils between the sex corresponded with the time when sex difference in susceptibility to *B. pahangi* infection was observed. These observations suggest that the high resistance to *B. pahangi* infection in female mice could be attributed to the high cellular responsiveness (macrophages and eosinophils) in females, because macrophages and eosinophils have been identified as important effector cells for filarial worm (Higashi and Chowdhury, 1970; Mehta *et al.*, 1981; Haque *et al.*, 1982; Chandrashekar *et al.*, 1985; 1986). Therefore, the differences of these cellular responses between sex seem to correlate with the expression of the differential sex susceptibility to *B. pahangi* infection in the BALB/c mouse. Antibodies seem to have a minor role on the expression of sex difference in susceptibility to *B. pahangi* infection. The complement−dependent antibody−independent cell−mediated killing of *B. pahangi* and *B. malayi* larvae have been reported (Chandrashekar *et al.*, 1985; 1986).

In contrast to a primary infection, sex difference was not observed in a challenge infection (Fig. 5). This result clearly indicates that sex difference in the susceptibility to *B. pahangi* infection in mice was induced only in a primary infection.

Recently, it has been reported that in *Strongyloides ratti* infection in C57BL/6 mice, sex difference in susceptibility (expressed as a higher susceptibility in males than in females, similar to *B. pahangi* infection in mice) was observed at the early tissue migratory phase of a primary infection (Kiyota, 1984; Kiyota *et al.*, 1984). More recently, Abe *et al.* (1985) reported that mononuclear phagocyte system played an important role on the expression of the resistance of female C57BL/6 mice to infection with *S. ratti*. Chandrashekar *et al.* (1986) reported that eosinophil enhances macrophage functions in the killing of *B. malayi* larvae. These reports suggest that different degree of effector cells not only in population kinetics but also in functions may alter the susceptibility to *B.*

pahangi infection in BALB/c mice. It may cause a differential sex susceptibility as a result. Therefore, the sex difference in functions of effector cells such as macrophages or eosinophils should be further clarified.

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BALB/c マウスにおける *Brugia pahangi* 感染感受性の性差
—エフェクター細胞の反応の性差について—

中西弘有（長崎大学医学部医動物学教室）

雄・雌 BALB/c マウスにおける *Brugia pahangi* 感染感受性の性差について検討した．感染幼虫（L3）50隻，マウス腹腔内接種後の虫体回収率の動態を調べてみると，初感染時には感染後比較的早い時期（5−10日）より感受性の性差（雄マウスの回収率は雌マウスに比し高い）が出はじめ，少なくとも感染後7週まで継続した．フィラリア虫体は 7−10 日という時期に脱皮し虫体の発育ステージを変える事より，いずれのステージの虫体が性差の発現に重要かを検討した．第4期幼虫移入時には性差は認められず，L3移入時のみ性差が認められた．これらの事から，初感染時の性差の発現には L3（あるいは脱皮ステージの虫体も含む）が最も関与している事が明らかとなった．次に再感染時に性差が出現するか否か検討した．雄・雌マウスとも初感染時に比し著しい虫体回収率の減少を示したが，再感染時の雄・雌マウス間では回収率に性差は認められなかった．この事から，マウスにおける性差の発現には初感染時の雄・雌マウス間の虫体に対する比較的早い時期の免疫応答の差が重要な要素であると考えられた．そこで感染後の抗体産生と腹腔内滲出細胞の変動を雄・雌マウス間で比較してみると，性差の出現する時期の 5−10 日においては IgG, IgM, IgE の抗体価には性差は認められなかったが，腹腔滲出細胞の動態，特にマクロファージ（Mφ）と好酸球（Eos）数には著しい性差が認められた．すなわち，感染抵抗性の強い雌マウスの Mφ，Eos 数は感染感受性の高い雄マウスに比し有意の増加が認められた．この事から *Brugia pahangi* 初感染初期の性差の発現には抗体よりは Mφ，Eos が重要な役割を担っていると考えられた．

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