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Activities of brush border membrane bound enzymes of the small intestine in *Metagonimus yokogawai* infection in mice

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Abstract: The present study intended to evaluate the influences of *Metagonimus yokogawai* on the activities of brush border membrane bound enzymes of the small intestine. Mice were infected with 500 metacercariae respectively, and the worm recovery, morphological changes and enzyme activities were observed chronologically. A part of them were followed after the treatment. Recovered worms decreased in number continuously after the infection, and they were less than 10% after 2 weeks and almost zero after 28 weeks. Villous atrophy and stromal inflammation were found at two locations of the proximal jejunum from 2 weeks to 4 weeks after the infection. The enzymes, alkaline phosphatase, leucine aminopeptidase and disaccharidases (sucrase, lactase, maltase, and trehalase), showed lowered activities in the duodenum and proximal jejunum of the infected mice but they increased in the distal jejunum for the first two weeks. From three weeks after the infection, the activities were gradually recovered. In one week treated mice, they recovered the activities at 2 weeks from the treatment, but there found no differences of the activities between the 3 week treated group and infected controls. The present data reveal that *M. yokogawai* infection induces degenerative changes of the host's intestinal mucosa not only morphologically but functionally during the initial phase of infection. The lowered enzyme activities in acute metagonimiasis should be associated with malabsorption and diarrhea.

Key words: *Metagonimus yokogawai*, mouse, small intestine, recovery, morphology, activities of brush border membrane bound enzymes, malabsorption

INTRODUCTION

Metagonimiasis is one of the major trematodiases of humans in Korea. Already we know many endemic areas are scattered throughout the country. The number of infected population is rather stationary in spite of public marketing of praziquantel which has specific anthelmintic efficacy on the flukes. That's because people prefer raw fragrant sweetfish. The main clinical symptoms of metagonimiasis are diarrhea and abdominal pain (Chi *et al.*, 1988; Chai *et al.*, 1989). However, it is still not well known how these symptoms are made. At present, some histopathological studies are available which observed morphological degeneration of the

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small intestine (Chai, 1979; Lee *et al.*, 1981; Kang *et al.*, 1983; Rho *et al.*, 1984). Those studies had shown that the small intestine of *Metagonimus* infected animals underwent villous atrophy, stromal inflammation, and crypt hyperplasia. According to the degenerative change of mucosa, mucosal absorption was suggested to be impaired. Mechanical destruction by the worms may partly devote to the change, and in addition to it immunological or biochemical factors should be considered.

The brush border membrane of the small intestinal epithelial cell contains many enzymes for final digestion, such as disaccharidases (sucrase, maltase, lactase, and trehalase), peptidases (aminopeptidase N, dipeptidyl aminopeptidase IV, and γ-glutamyl transpeptidase), and alkaline phosphatase (Dawson & Davies, 1963; Forstner *et al.*, 1968; Fujita *et al.*, 1972). It is already proved that the brush border enzyme activities are reduced as the villous epithelial cells are destroyed in coeliac disease (Andersen *et al.*, 1983), peptic ulcer (Kim *et al.*, 1986), *Bacteroides* sp. infection (Riepe *et al.*, 1980) and giardiasis (Sood *et al.*, 1987). The only fluke that is known to lower activities of such enzymes is *Fibricola seoulensis* (Hong *et al.*, 1991).

We have investigated the effect of *Metagonimus* infection on activities of brush border membrane bound enzymes of the small intestine as well as the worm recovery and morphological change, and thus to figure out the impact of metagonimiasis on intestinal function of digestion or absorption. The enzymes are disaccharidases (sucrase, maltase, lactase, and trehalase), L-leucine aminopeptidase and alkaline phosphatase.

MATERIALS AND METHODS

1. Collection of metacercariae of *M. yokogawai* and infection to mice

The mice, 15~20 g in body weight of ICR strain, were purchased from the Animal Colony of Seoul National University and the mice were treated with praziquantel, mebendazole and metronidazole for two weeks, and used for the experiment.

Metacercariae of *M. yokogawai* were procured from naturally infected sweetfish (*Plecoglossus altivelis*) which had been caught from an endemic area of this infection, at the Sumjin River basin in Hadong-gun, Kyongsangnam-do. By artificial peptic digestion technique, the metacercariae were isolated. Collection and counting of the metacercariae were done under a stereomicroscope. The mice were divided into 4 groups; one, being uninfected control; the second, infection group (infected but not-treated); the third, treated at 1 week of infection group (treatment group I); the fourth, treated at 3 weeks of infection group (treatment group II). Five hundred metacercariae were infected to each mouse. Mice of the control or infection groups were sacrificed at 3, 7, 10, 14, 21, 24, 28, 35 and 42 days after the infection. The mice of treatment group I were sacrificed at

Table 1. The numbers of mice used for the experiment

Days from inf.	Uninfected control	Infected control	Treatment Group I*	Treatment Group II*
For enzyme activities				
3	5	10		
7	5	10		
10	5	11	9	
14	5	9	9	
21	5	7	10	
24	5	8		8
28	5	7		8
35	6	7		8
42	6	5	9	7
For worm recovery				
3		5		
7		5		
10		5	1	
14		2	2	
21		3	1	
24		3		1
28		3		1
35		3		1
42		2	1	1

* Treatment Group I was treated at 1 week, and Group II was at 3 weeks after the infection.

3, 7, 14 and 35 days after the treatment, and the mice of treatment group II were at 3, 7, 14 and 21 days after the treatment (Table 1). A part of the animals in each group were shared for the worm recovery and histological observation.

2. Worm recovery

The mice for worm recovery were as presented in Table 1. Their small intestine was resected and the lumen was opened and dipped in 0.85% cold physiologic saline for 2 hrs to make the worms detached from the mucosa. The freed worms were all collected and counted.

3. Histopathological examination

Two mice per each group were preserved for pathological observation. Two segments of the proximal jejunum, one 5 cm from Treitz's ligament(JI) and the other 5 cm distal from the first one(JII), were fixed in 10% neutral formalin. The fixed tissues were dehydrated by successive changes of alcohols, cleared in three changes of xylene, embedded in paraffin, and sectioned in 4 micrometer thickness. Routine haematoxylin and eosin staining was done.

4. Tissue processing for enzyme activity assay

The entire length of the small gut from the pylorus to the ileo-cecal(IC) junction was removed and divided into three segments; the duodenum, proximal jejunum (proximal one-third of small intestine from the Treitz's ligament to the IC junction) and remaining part as distal jejunum. Each of the intestinal segments was rinsed with ice-cold physiologic saline and the mucosal layer was collected by scraping with a slide glass on the ice chamber. The scrapeds were homogenized for 1 minute by a teflon homogenizer (Tri-R Stir-R, Model S63C, Tri-R instruments, Inc., NY) in 30 vol. of 0.05 M mannitol-2 mM Tris HCl buffer (pH 7.0). The concentration of $CaCl_2$ of the homogenate was made 10 mM by adding 0.4 M $CaCl_2$. The mucosal homogenate was sonicated by a sonicator (®Model W-380, Heatsystem-Ultrasonics, INC, NY) for 30 seconds.

5. Enzyme activity assays

1) Alkaline phosphatase

Alkaline phosphatase activity was assayed using *p*-nitrophenyl phosphate as substrate at pH 10.0. The reaction mixture contained 190 mM $NaHCO_3$ and 4 mM substrate, and incubated for 30 min at 37°C. The reaction was stopped by adding 2.5 ml of 0.02 N NaOH, and absorbance was measured at 400 nm with a spectrophotometer (Uvikon spectrophotometer, Kontron instruments, Zürich).

2) Leucine aminopeptidase

Aminopeptidase activity was measured using L-leucin-B-naphthylamide HCl as substrate. Mucosal homogenates were mixed with 72.5 mM PBS buffer (pH 7.0) and 325 mM substrate and incubated for 15 min at 37°C. In the ice bath, the reaction was stopped by adding of 300 μl of 32% TCA and 100 μl of 0.3% $NaNO_2$. Then 100 μl of 1.5% ammonium sulfamate and 300 μl of NEDA were added for the color reaction. Absorbance was measured at 560 nm.

3) Disaccharidases

Lactase, sucrase, maltase, and trehalase activities were determined in each specimen by the method of Dahlqvist(1968). The 0.056 M substrate buffer solutions were made by mixing of 0.1 M sodium maleate buffer, pH 6.0, and the disaccharides. TGO(tris glucose oxidase o-dianisidine reagent) solution was made with 100 ml of 0.5 M tris HCl buffer (pH 7.0), 4 mg of glucose oxidase, 0.5 mg peroxidase, and 100 mg o-dianisidine. This solution was stabilized for 3 days at 4°C before use. The substrate buffer solutions of 50 μl and same volume of mucosal homogenates were mixed and incubated for 30 min at 37°C for substrate hydrolysis. Then for color reaction, 1.5 ml of TGO solution was added. After 30 min incubation at 37°C, 0.75 ml of 50% H_2SO_4 was added to stop the reaction. Absorbances were measured at 530 nm.

4) Enzyme activity units

The activities of all enzymes were given in units, one unit was corresponding to the hydrolysis activity of 1 μmol substrate per minute at 37°C. Protein was measured by the modified method of Lowry *et al*(1951).

RESULTS

1. Worm recovery

The worm recovery rate was rapidly declining after infection, and less than 10% after 2 weeks and nearly zero after 4 weeks from infection. The mean numbers of recovered worms per mouse were shown in Fig. 1.

2. Histopathological examination

The histopathological changes were more intensive at JII region than JI. Villous changes such as fusion, tip blunting and shortening appeared from 1 week and profound at 2 or 3 weeks. Crypt hyperplasia was accompanied by villous changes, and vascular ectasia and edema in stroma was observed by 4 weeks after infection. Inflammatory cell infiltration in stroma was not so conspicuous that only a few plasma cells and/or eosinophils were in the stroma. From 3 weeks(JI) to 6 weeks(JII), microscopic changes in mucosa were recovered(Table 2).

3. Changes of enzyme activity in the duodenum(Fig. 2)

1) Alkaline phosphatase

On 3 to 10 days after infection the enzyme activity decreased and recovered in the following period. The activities of treatment group I showed no changes compared with those of untreated control, but the treatment group II showed slightly increasing activities.

2) Leucine aminopeptidase

The activities of infected mice generally decreased. In case of treatment group I, the activity was decreased for the first 2 week but at 5 weeks the activity was significantly increased to uninfected control level. The treatment group II showed no difference in the enzyme activity with untreated group.

3) Sucrase

The activity of infected mice showed no change from that of control group. By the first week after treatment in group I, the activity decreased, but the difference was recovered at the following period.

4) Lactase

The activity of lactase decreased at 21, 24, 28 days after infection but the difference disappeared at the following period.

5) Maltase

The activity of maltase decreased during the infection period by the 6th week. In the treatment group I, its activity decreased by the 2nd week after treatment, but recovered to that of untreated group at 5 weeks. At the third day in the treatment group II, the activity

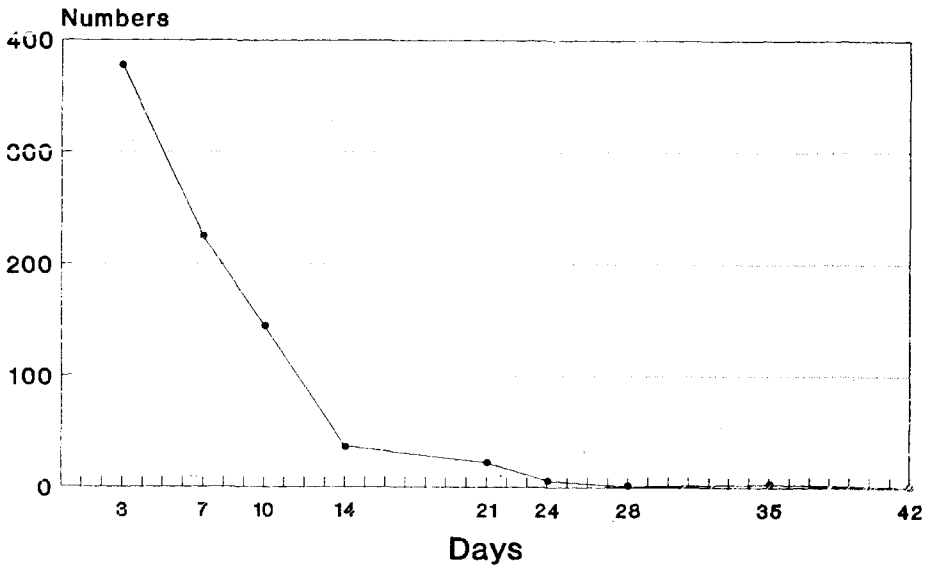

Fig. 1. The mean numbers of recovered worms per mouse.

Table 2-1. Microscopic findings of the jejunal mucosa(JI)* by the duration of infection and treatment

Days	Villus			Crypt	Stroma		
	fusion	blunting	atrophy	hyperplasia	vasc. ectasia	edema	cell infilt.
Infected control							
3	−	−	−	−	±	±	−
7	−	−	±	−	±	±	±
14	+	+	+	+	+	+	+
21	+	+	+	−	+	+	−
24	±	−	−	−	−	−	−
28	−	−	−	−	−	−	−
35	−	−	−	−	−	−	−
42	−	−	−	−	−	−	−
Treatment Group I							
7	−	−	−	−	−	−	−
14	−	−	−	−	−	−	−
35	−	−	−	−	−	−	−
Treatment Group II							
3	−	−	−	−	−	−	−
7	−	−	−	−	−	−	−
14	−	−	−	−	−	−	−
21	−	−	−	−	−	−	−

+: changed ±: slightly changed −: unchanged
* This part is 5 cm distal from the Treitz's ligament.

Table 2-2. Microscopic findings of the jejunal mucosa(JII)* by the duration of infection and treatment

Days	Villus			Crypt	Stroma		
	fusion	blunting	atrophy	hyperplasia	vasc. ectasia	edema	cell infilt.
Infected control							
3	−	−	−	±	−	−	−
7	±	−	+	−	+	+	+
14	+	+	+	+	+	+	+
21	+	+	+	±	+	+	−
24	+	+	+	+	±	−	−
28	+	+	+	+	±	±	−
35	+	+	+	±	−	−	−
42	−	−	−	−	−	−	−
Treatment Group I							
7	±	−	−	±	±	±	−
14	±	−	−	−	−	−	−
35	−	−	−	−	−	−	−
Treatment Group II							
3	±	±	±	−	±	±	−
7	+	+	+	±	+	+	−
14	−	−	−	−	−	−	−
21	−	−	−	−	−	−	−

+: changed ±: slightly changed −: unchanged
* This part is 15 cm distal from the Treitz's ligament.

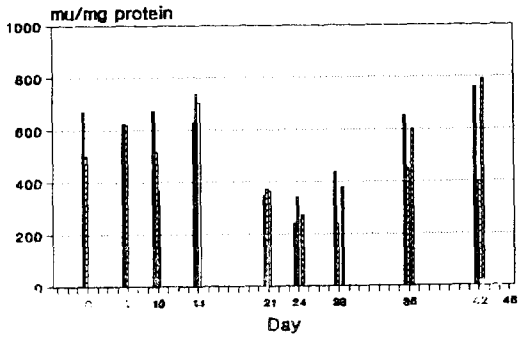

Fig. 2-1. Alkaline phosphatase

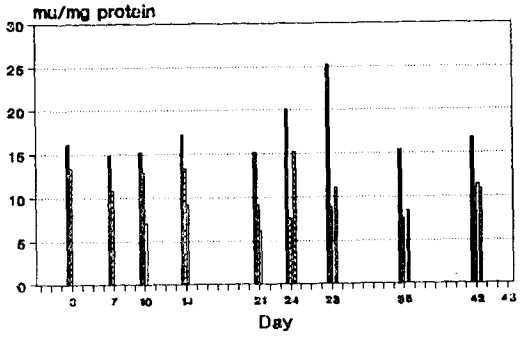

Fig. 2-2. Aminopeptidase

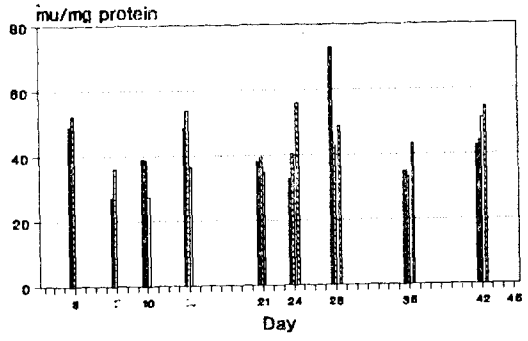

Fig. 2-3. Sucrase

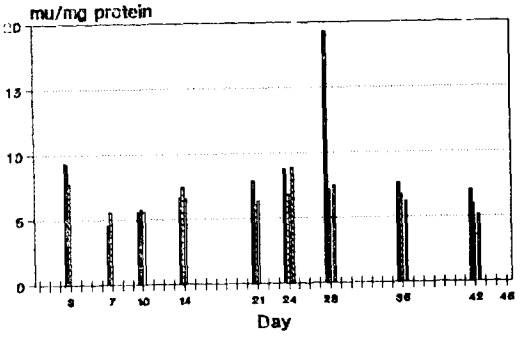

Fig. 2-4. Lactase

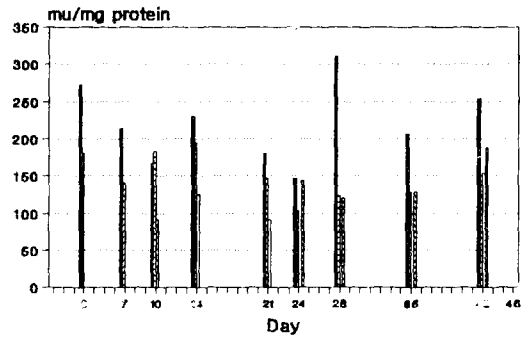

Fig. 2-5. Maltase

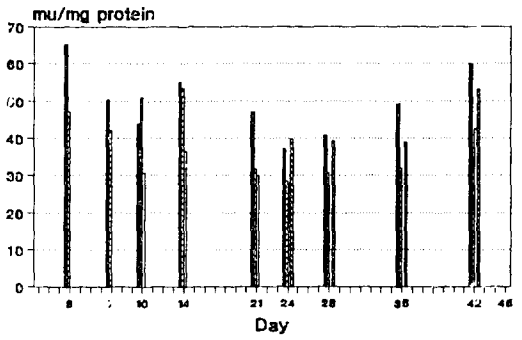

Fig. 2-6. Trehalase

Fig. 2. The enzyme activities in the duodenum of mice.

began to increase and returned to that of untreated group at the following period.

6) **Trehalase**

The activity was reduced 3 days or 3 weeks after infection. The activities of both treatment groups increased rapidly to those of untreated mice.

4. Enzyme activity changes of the proximal jejunum (Fig. 3)

1) **Alkaline phosphatase**

The activity of infected group decreased at the first week after infection and restored to the control level after then.

2) **Leucine aminopeptidase**

At 3, 7 and 42 days after infection, the acti-

vity decreased significantly. In the treatment Group I, the activity remained low by the second week but it was recovered at 5 weeks after treatment. In the treatment Group II, the activity was elevated at the first week.

3) **Sucrase**

By the second week after infection the activity decreased, and returned to normal thereafter. The activity of the treatment group I began to resume the control level after one week from treatment. In the treatment group II, the activity increased at the second week.

4) **Lactase**

The activity of the infection group was reduced during all infection period. The activity of the treatment group I decreased at 1 and 2

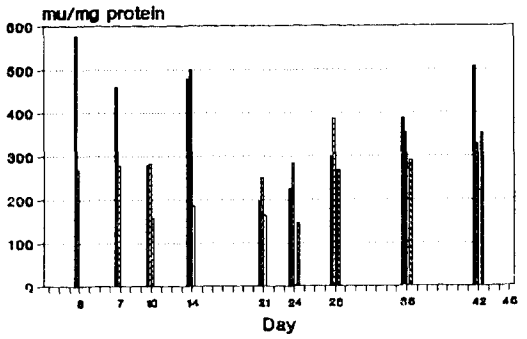

Fig. 3-1. Alkaline phosphatase

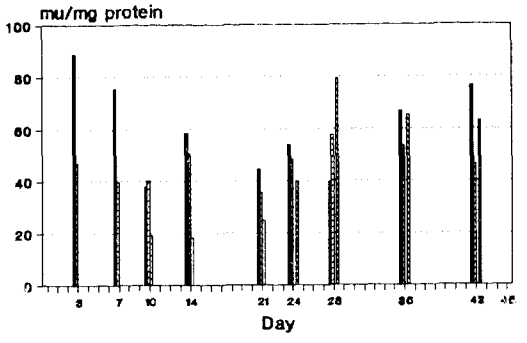

Fig. 3-2. Aminopeptidase

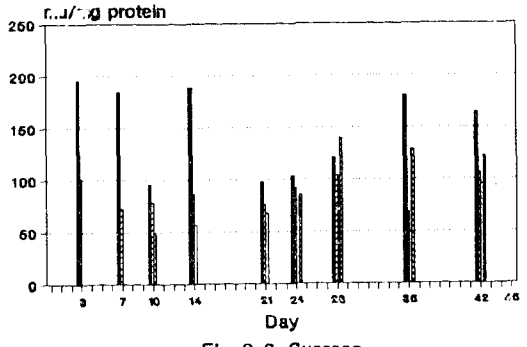

Fig. 3-3. Sucrase

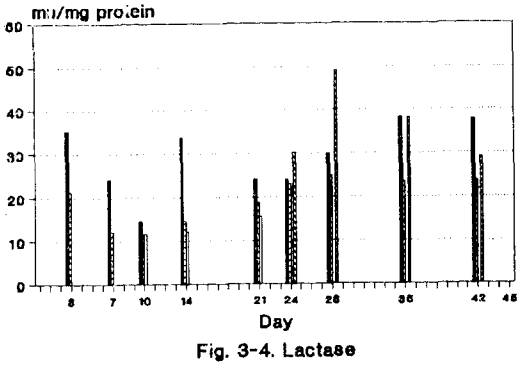

Fig. 3-4. Lactase

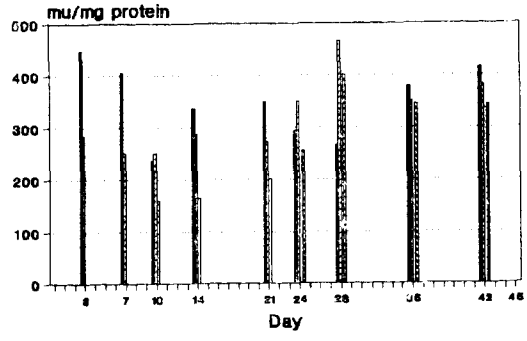

Fig. 3-5. Maltase

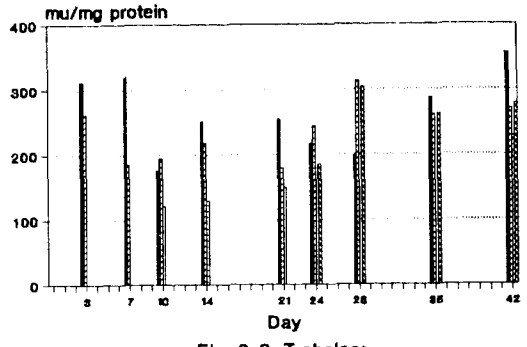

Fig. 3-6. Trehalase

Fig. 3. The enzyme activities in the proximal jejunum of mice.

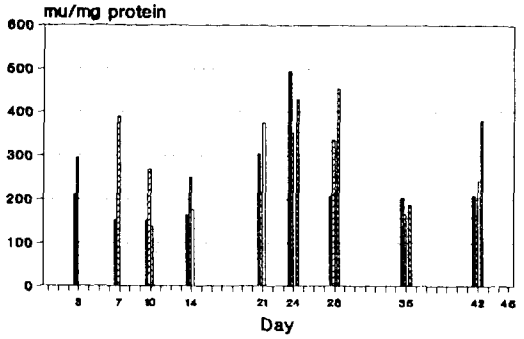

Fig. 4-1. Alkaline phosphatase

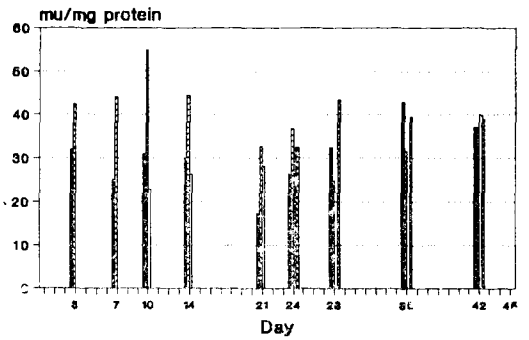

Fig. 4-2. Aminopeptidase

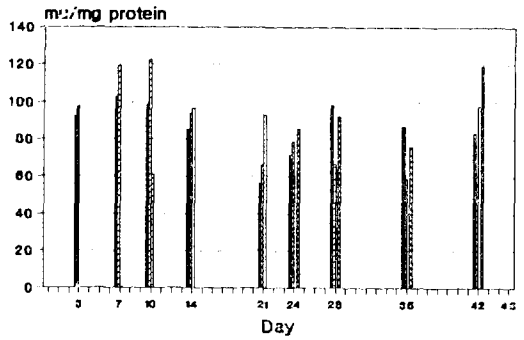

Fig. 4-3. Sucrase

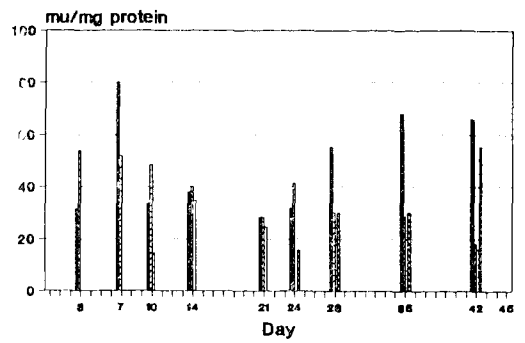

Fig. 4-4. Lactase

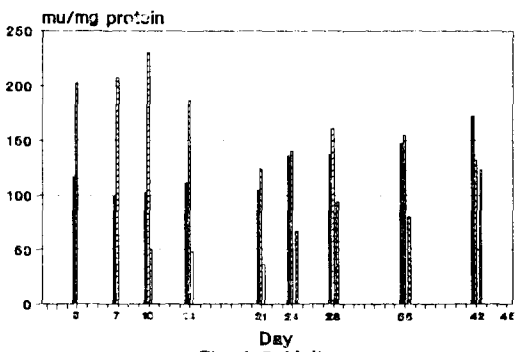

Fig. 4-5. Maltase

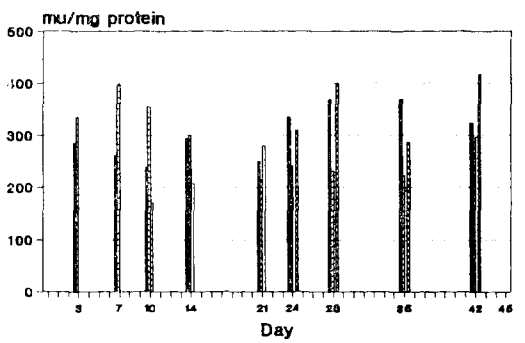

Fig. 4-6. Trehalase

Fig. 4. The enzyme activities in the distal jejunum of mice.

weeks after treatment, and in the treatment group II, the increased activity was shown at the first week after treatment.

5) **Maltase**

The activity decreased at 3 and 7 days after infection. And decreased activity was observed at 3, 7, 14 days after treatment at 1 week. In the treatment group II, no activity difference was noticed with untreated group.

6) **Trehalase**

By the early 7 days, the activity of infection group was reduced but not recovered distinctively in the treatment group

5. **Enzyme activity changes of the distal jejunum** (Fig. 4)

1) **Alkaline phosphatase**

Increased activity appeared at 3, 7, 10 days after infection. In the treatment group I, there was no significant difference with control group.

2) **Aminopeptidase**

The activity of infection group initially increased by 24 days after infection, and decreased at following days. The activity was recovered to control level when the mice were treated.

3) **Sucrase**

The activity initially increased by the second week after infection, but decreased later. The activity was recovered to control level when the mice were treated.

4) **Lactase**

After 28 days of infection its activity decreased. The activity of the treatment group I was almost same with that of untreated group, but the activity of the treatment group II increased to control level at 3 weeks.

5) **Maltase**

By the third week after infection, the activity increased significantly, and reduced to normal control level after then. The activity of the treatment group I significantly decreased, and the activity of the treatment group II was lowered in the early stage but recovered to the control level at 3 weeks after treatment.

6) **Trehalase**

The activity increased at early infection period, but after 21 days of infection it decreased significantly. The activity of the treatment groups didn't show any significant difference with that of the control group.

DISCUSSION

A few previous studies have revealed impaired activities of intestinal brush border enzymes in infections of some parasites such as *Giardia* (Sood *et al.*, 1987) or *Fibricola seoulensis* (Hong *et al.*, 1991). Also decreased activities of the enzymes were found in other degenerative diseases of the intestine (Riepe *et al.*, 1980; Andersen and Skagen, 1983; Kim *et al.*, 1986). Because *Metagonimus* is known to make severe degenerative changes in the mucosa of the small intestine (Chai, 1979; Lee *et al.*, 1982; Kang *et al.*, 1983; Rho *et al.*, 1984), it is also expected to change activities of the enzymes.

In the present study, activities of the brush border membrane bound enzymes showed different patterns by the duration of infection, treatment period, intestinal locality or the enzymes. In the duodenum, activities of alkaline phosphatase, L-leucine aminopeptidase, maltase and trehalase were reduced in early infection stage. In contrast, sucrase and lactase activities showed no differences, probably because these enzymes originally exist too little amount in the duodenum to be significant (Newcomer & McGill, 1966). In the proximal jejunum, activities of sucrase, trehalase, maltase, and lactase were all decreased just after the infection, and those of maltase and trehalase were recovered after 3 weeks. By histopathological findings, the morphological change of villous layer was most severe in this part of the intestine especially in acute phase of infection. The morphologic degeneration should be followed by changed activities of the enzymes. In contrast to the two proximal parts of the intestine, activities of all enzymes at the distal jejunum were increased in early infection period. We think that this phenomenon may be a compensatory reaction due to increased concentrations of the substrates in the lumen of the distal jejunum by reduced activities in the duodenum or proximal jejunum as Raul *et al.* (1988) suggested.

Rho *et al.* (1984) described that young *Metagonimus* invaded into the crypt layer just after hatching from the metacercariae. The invasion may directly damage the enterocytes at the upper layer of the crypt where the enzymes are produced (Becciolini *et al.*, 1987). Furthermore, the turnover rate of villous epithelial cells might be enhanced according to increased exfoliation of the cells, and thus immature enterocytes might cover the villi. Full activities of the enzymes are expressed as the cells are mature (Raul *et al.*, 1988). In this context, the proximal jejunum which is the main habitat may lose the enzyme activity most

distinctively by the infection of *M. yokogawai*. In addition to the immaturity of cells, reduction of mucosal surface area by atrophic change also involves lowering the activities. These are the host factors. However, there is no clue for any parasite factor on the enzyme activities. For this point, a few reports have mentioned direct influence of secretes from some bacteria. Cholera toxin, for example, was found to inhibit the activity initially but to stimulate after 16 hours (Miura *et al.*, 1982). The effect was known to be mediated by inhibition of adenyl cyclase at the brush border. The possibility of any eventual influence of metabolic secretes from *Metagonimus* on the enzyme activity cannot be excluded. This should be a subject of further study.

When the mice were treated with praziquantel after one week, the enzymes maintained low activities by 2 weeks from treatment but returned to untreated control level after then. The mice treated at 3 weeks after infection showed little difference in the enzyme activities with the infected control. Actually the activities of most enzymes resumed control level after 3 weeks from infection in the infected not-treated mice. Because the mouse itself is not such a suitable host of *Metagonimus*, self cure phenomenon is observed naturally in early stage of infection as well as low infection rate (Chai *et al.*, 1984). The present recovery of worms showed less numbers than 10% after 2 weeks and almost zero after 4 weeks. Such a rapid elimination of worms from the intestine enables rapid restoration of the enzyme activities after infection without treatment. Resuming the enzyme activity requires about 2 weeks in mice which were treated after one week of infection. This healing period after treatment is same as Hong *et al.* (1991) observed in *Fibricola* infection. In the histopathological findings, mainly plasma cells and eosinophils were in the villous stroma up to 3 weeks. Villous atrophy in proximal jejunum was found also by 3 weeks after infection. The period showing inflammation and villous atrophy is same with that of lowered activities of the enzymes. At later stage than 3 weeks, treatment showed no effect because the enzyme activities were under healing process already. Furthermore, probably host immune reaction begins to be effective at this 3 weeks after infection. Therefore, this is the turning point of diminished enzyme activities to resume the control level.

There have been no data for the effect of praziquantel on the enzyme activities. Although the present study had no praziquantel control, we could exclude the influence because toxicologic studies of praziquantel showed no organic nor functional impairment in its therapeutic dose of 10mg/kg (Andrews *et al.*, 1983).

Cho *et al.* (1985) investigated that the intestinal content of dogs with metagonimiasis was isotonic because villous distortion inhibited absorption of secretion from crypts. The present data suggest that diminished activities of brush border enzymes in metagonimiasis may inhibit digestion of small molecules on the brush border, and consequently cause absorption disturbances through the membrane of enterocytes. The decreased activities of the brush border membrane enzymes should be one cause of diarrhea in metagonimiasis.

Interpretation of the present data has some limitations. First, the activities of the present enzymes showed wide fluctuations even in the control. Also the activities varied by individual enzyme. Therefore, we should adopt the changing patterns but not the absolute units of the activities. Also if other suitable hosts than mice such as dogs or cats had been used, they would have shown distinctive patterns. Furthermore the number of infected metacercariae seemed not so enough that more dramatic results were induced. None the less it is worthwhile to note that the present study supplies basic informations as an experimental model for the impact of the trematode infection on functions of the small intestine.

Conclusively, in mouse metagonimiasis, the activities of disaccharidases, alkaline phosphatase and L-leucine aminopeptidase decreased

in early stage of infection in the duodenum and proximal jejunum, but increased in the distal jejunum. They began to resume the activities about 3 weeks after the infection and praziquantel treatment showed little effect in the period of recovery if treated 3 weeks after the infection. Metagonimiasis must impair the digestion and absorption on the brush border, and consequently evoke osmotic diarrhea.

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=국문초록=

요꼬가와흡충에 감염된 마우스 소장의 미소융모막 효소 활성도

서울대학교 의과대학 풍토병연구소 및 기생충학교실, 한국원자력병원 병리과*
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요꼬가와흡충은 국내에서 가장 감염이 흔한 장흡충으로 은어나 기타 담수어에 의해 매개되며 전국적으로 분포한다. 이 흡충에 감염되면 심한 설사를 하며 이때 소장의 점막이 퇴행성 변화를 보인다. 이 연구에서는 소장 상피세포의 미소융모막에 분포하는 몇 가지 소화효소의 활성도가 요꼬가와흡충의 감염과 치료에 의하여 받는 영향을 관찰하였다. 그 결과를 보면 이 흡충에 감염되면 충체가 빠르게 배출되어 감염 2주 이후에는 투여량의 10% 이내의 충체만이 감염되어 있고, 상부 공장에서 감염 2~4 주에만 퇴행성 변화와 염증반응이 관찰되었다. Alkaline phosphatase, leucine aminopeptidase, disaccharidases (sucrase, maltase, trehalase, lactase)의 활성도가 십이지장과 상부 공장에서 감염 2주까지는 감소하였으며 하부 공장에서는 증가하였다. 감염 3주 이후에는 감염군에서의 활성도가 정상 대조군의 것과 차이가 없었다. 감염 1주에 치료한 군의 활성도는 치료 후 2주에 감염대조군의 활성도와 비슷한 수준으로 회복하였고, 감염 3주에 치료한 군은 치료를 안한 감염군과 같은 활성도를 보였다. 요꼬가와흡충에 감염된 마우스의 소장에서 초기에 미소융모막 효소의 활성도가 크게 감소하며, 이러한 변화는 형태학적인 병변의 생성 및 회복과 또한 감염된 충체의 수의 시기적 변화와 일치하였다. 요꼬가와흡충 감염 초기에 소장의 소화효소 활성이 감소하는 현상이 미소융모막에서 일어나는 소화 및 흡수를 저해하고 이에 따라서 설사가 초래되는 것으로 추정된다.

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