別紙様式第４

学　位　論　文　要　旨

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［論文題名］

X-ray evaluation of intestinal dysmotility induced by *Eimeria pragensis* infection in C57BL/6 mice
(C57BL/6マウスにおいてEimeria pragensis感染により生じた腸管運動障害に対するX線評価)

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［要　旨］

Abstract

Recently, anecdotal reports have arisen of eimeriosis in cattle resulted in delayed intestinal motility. Some observation from field veterinarians claimed that coccidiosis cattle discharged smaller amount of feces despite having normal feed intake. Some veterinarians who observed this issue considered the administration of prokinetic agent to alleviate the symptoms. However, direct evidence and related mechanisms of delayed intestinal motility of cattle with eimeriosis have been never reported. This study was conducted to elucidate the intestinal dysmotility during coccidiosis. We used murine Eimeria pragensis in this study as a model for mammalian eimeriosis. This species is a highly pathogenic Eimeria of mice, parasitizing at the caecum and excretion of oocyst starts from 7 days post-infection (d.p.i.).

To investigate whether E. pragensis can induce intestinal dysmotility, the whole intestinal transit time (WITT) of barium sulfate was measured in E. pragensis infected and uninfected mice. The WITT of infected mice at 7 d.p.i. was significantly longer (6 hr) than that of uninfected mice (2.5 hr), indicating the occurrence of intestinal hypomotility.

To identify the location of intestinal hypomotility, we measured gastrointestinal (GI) motility at 7 d.p.i. by contrast gastrography of barium sulfate of infected group in comparison with uninfected group. The intermittent gastrography study of uninfected mice revealed the half-life of barium in the stomach was approximately 2 hr after its administration. Also in those mice, the time required for the maximum filling of the small intestine, caecum, and colorectum was approximately 1 hr, 2 hr, and 6 hr, respectively. The intestinal motility pattern of infected mice was observed to be altered in the small intestine, caecum, and colorectum. The most prominent alteration was observed in the caecum of infected mice as the time required for emptying of this organ was extended to more than 48 hr. Besides this, the caecum showed the delayed start of barium filling probably because the barium was retained longer in the small intestine and reached later to the caecum. The barium filling and emptying in the colorectum of infected mice were altered in a similar fashion with those in the caecum.

As the main infection site of E. pragensis is the caecum, it would be logical to consider the intestinal dysmotility to occur in the caecum. However, the intermittent gastrography study revealed the delayed emptying of barium from the small intestine and thus indicated the hypomotility of the upper intestinal tract. The charcoal propulsion study at 7 d.p.i. confirmed this incidence. The charcoal propulsion was slower in infected group (reaching to 40.4% of the whole small intestine) compared to uninfected group (68.0%). This confirmation indicated the occurrence of systemic alteration on GI motility during E. pragensis infection.

To evaluate the onset of intestinal dysmotility occurrence in the course of E. pragensis infection, the intestinal motility was evaluated at prepatent period (4 d.p.i.), during patency (7 d.p.i.), and after patent period (14 d.p.i.). In this study, infected group was inoculated with 300 sporulated E. pragensis oocysts. Intermittent gastrographic observation was conducted at 6 and 12 hr after barium administration at the designated time of observation. The intestinal hypomotility in infected mice was observed at patent period, but not in prepatent or after patent periods. From this finding, we deduced that the intestinal dysmotility might have occurred in relation with the developmental stage of E. pragensis and subsequent damage resulting from its development.

From the post-infection time dependent study, we analyzed the infection-dose dependency of the occurrence of intestinal dysmotility. It was assumed that the intestinal dysmotility might have occurred due to the subsequent intestinal damage of E. pragensis development. Therefore, it was assumed that by increasing the infection dosage, a parallel increase of the intestinal dysmotility severity in the infected mice might be observed. Intestinal motility was evaluated in three infected groups with different inoculation doses of sporulated E. pragensis oocysts. The groups were assigned as Dose 100, Dose 300, and Dose 1000 groups and inoculated with 100, 300, and 1000 sporulated E. pragensis oocysts, respectively. Intestinal motility was evaluated semi-quantitatively at 7 d.p.i. by contrast gastrography with observation at 6 and 12 hr after barium administration. In the Dose 100 group, the intestinal dysmotility was only observed in the caecum. In the Dose 300 group, the intestinal dysmotility was observed in the caecum, but also in the small intestine and colon. As the infection dose became higher in the Dose 1000 group, the intestinal dysmotility occurred in the same sites with the Dose 300 group but for longer time in the small intestine. Accordingly, as the infection dose increased, the severity of intestinal motility became more prominent.

The delayed intestinal motility observed in the infected groups could be induced by another factors such as restraint stress or fasting. A similar restraint stress was applied in all groups including uninfected group of this study, and thus the observation that the intestinal dysmotility was only observed in infected mice could eliminate the possibility of restraint stress incurring in intestinal dysmotility. Therefore, we evaluated the effect of fasting and conducted the feed apprehension study to elucidate the consequence of low feed intake on intestinal dysmotility. In infected groups, we observed that the decrease of feed intake was started one day before oocyst shedding (6 d.p.i.). This reduction of feed intake may result in slower intestinal motility as previously reported. In this study, a fasting group was designed with limited feed intake, as low as half amount of daily feed intake of the control group and compared the intestinal motility of the infected and control groups. The transition of barium in the fasting group did not show significant difference from that of uninfected group. After eliminating restraint stress and fasting as a possible cause to intestinal hypomotility, it was deduced that intestinal dysmotility in infected group was induced by the infection of E. pragensis in the intestinal tissue.

In summary, it was revealed the evidence of intestinal hypomotility during coccidiosis. Eimeria pragensis infection in the caecum of the mice induced systemic hypomotility in the small intestine, caecum, and colorectum which could be observed from the onset of oocyst excretion and by dose-dependent manner. We proposed this newly observed clinical symptom in coccidiosis as coccidiosis intestinal dysmotility (CID). This finding is fundamental to re-evaluate the clinical manifestations of coccidiosis in another species.

備考　論文要旨は、和文にあっては 2，000 字程度、英文にあっては 1，200 語程度