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two animals responded to DTSKFTPTVAHRLKHAEDLF⁹², and that from another animal responded to

GTGKWDFVCNFKVTKVKFE¹⁸². In the regions of MPSP containing these epitopes, diversities were found among four types of the MPSP.

Gastric mucosal hyperplasia and hypergastrinemia in rats and mice heavily infected with *Taenia taeniaeformis* larvae

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Rats heavily infected with *Taenia taeniaeformis* larvae in the liver show a remarkable increase in their stomach weight and intragastric pH, hyperplasia of the gastric mucosa accompanied by mucous cell proliferation, decrease in number of chief cell and parietal cell and hypergastrinemia. These characteristics are similar to those of some human conditions such as Zollinger-Ellison syndrome, Menetrier's disease (MD), hypertrophic hypersecretory gastropathy. *T. taeniaeformis* /rat system can be a candidate model for such human gastrointestinal diseases and others with hypergastrinemia. However, there is not enough detailed report to make comparison with these diseases. Hence, the pathological changes of the gastric mucosae were examined in rats heavily infected with *T. taeniaeformis* larvae using light and electron microscope.

In the infected rats, gastric mucosal hyperplasia began to be observed at 56 days postinfection (DPI), the structural disturbance of zymogenic units in the corpus and mucous units in the antrum had increased with time. In the corpus, after 56 DPI, four types of alcian blue (AB) and/or Periodic acid Schiff (PAS) -positive mucous cells increased in their numbers around hyperplastic gastric glands. At 56 DPI, two types of those mucous cells were observed using electron microscope, one was type I cells, which

were rectangle in shape, whose cytoplasm was occupied by a few large secretory granules and a few small granules, and another was type II cells, which were square in shape, and its cytoplasm contained many secretory granules. At 70 DPI, along with type I and II, type III cells, which was square in shape and contained some secretory granules, were observed. Type IV cells, which were ovoid in shape containing some granules, were observed at 84 DPI. Contrary to these increases, zymogenic and parietal cells decreased in their numbers, which continued to 112 DPI. Apoptotic bodies also started to appear after 56 DPI at the corpus and the antrum and increased in their numbers with the time of the infection.

The infected rats showed increase in the serum concentration of alanine aminotransferase and aspartate aminotransferase, which suggested some damage to the host's liver. Decrease in the concentration of serum total protein was also observed, which was also known to occur in patients with MD. These histopathological and blood biochemical findings strongly suggested that *T. taeniaeformis* /rat system could become a candidate model for human gastrointestinal diseases such as Zollinger-Ellison syndrome, MD, hypertrophic hypersecretory gastropathy.

The gastric mucosal hyperplasia was observed ultrasonographically prior to the onset

of hypergastrinemia, which suggested that the hyperplasia was not due to the effect of gastrin in rats heavily infected with *T. taeniaeformis* larvae.

There were various suggested causes of MD and one of them is concerned with transforming growth factor alpha (TGF alpha). TGF alpha has physiological functions similar to epidermal growth factor (EGF) and shares a receptor with EGF. EGF is largely secreted from submandibular glands in rats. Hence, rats with their submandibular glands surgically excised were orally infected with *T. taeniaeformis* eggs, and their gastric mucosa and the larvae were examined histopathologically and immunohistochemically using antibodies against TGF alpha and EGF.

Gastric hyperplasia were observed in both sialoadenectomized and non-sialoadenectomized rats infected with *T. taeniaeformis* larvae. Furthermore, the gastric mucosa and the larvae were not immunostained neither with anti-EGF antibody nor TGF alpha antibody. These results suggested that EGF was not concerned with the gastric hyperplasia. The results of immunostaining using anti-TGF alpha was different from that of MD where those gastric mucous cells around the dilated gastric glands were heavily immunostained with anti-TGF antibody, suggesting that pathogenesis of the rats heavily infected with the larvae was somewhat different from that of MD.

T. taeniaeformis larva infects host's liver, and the infection causes disorder of the host's liver. Hepatocyte growth factor (HGF) is a hepatotrophic factor for liver regeneration, heavily released from the injured liver to accelerate the healing process, and has the mitogenic effect on various epithelial cells including gastric and esophageal epithelial cells. To decrease the larval influence to the rat's liver, the larvae were collected from the donor rats, and 136-300 of the larvae were implanted into the intraperitoneal cavity of uninfected rats (recipient rats), which

were examined blood-biochemically, ultrasonographically and histopathologically.

Though variation was observed in the mucosal changes of recipient rats, 5 of 7 recipient rats showed hyperplasia accompanied with mucous cell proliferation, and 2 showed hypergastrinemia. These results suggested that gastrin and HGF were not important for the gastric mucosal hyperplasia, and it was caused by the larval excretory-secretory product.

Several other rodents are known to become intermediate hosts for *T. taeniaeformis*. However, the gastric hyperplasia and/or hypergastrinemia have not been reported to occur in other than the heavily infected rats. Several strains of mice which were known to be sensitive to *T. taeniaeformis* infection and Belgium mouse strain of *T. taeniaeformis* which were originally isolated from a house mice *Mus musculus* were selected for the experiment. AKR/N and C3H/He strains, and BALB/cA-RAG2^{-/-} strain which can not produce mature B and T cells because of lack of gene RAG2, were orally inoculated with *T. taeniaeformis* eggs and examined histopathologically and blood-biochemically.

AKR/N and C3H/He did not show any changes in gastric mucosa and serum gastrin level even though the established infection in their liver was heavy. However, infected BALB/cA-RAG2^{-/-} mice at 56 DPI and 112 DPI showed some gastric mucosal hyperplasia accompanied by mucous cell proliferation and decrease in number of chief cells and parietal cells. These histopathological changes were similar to those of the infected rats. Though hypergastrinemia was not observed in the BALB/cA-RAG2^{-/-} mice, these findings suggest that this *T. taeniaeformis*/mouse system may make a good advances for the research of the cause and the mechanism, because mouse is smaller than rat and less dose of the excretory/secretory products from the larvae may cause hyperplasia in infected mice.

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Clinicopathological studies on atrial and brain natriuretic peptide in canine heart disease

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In small animal medicine, there has been an increase in the number of canine patients diagnosed and treated for heart diseases. A more accurate recognition of the pathophysiology of canine heart diseases allows for a better and more appropriate therapeutic selection which may improve quality of life and reduce mortality from canine heart diseases.

In human cardiovascular medicine, cardiac hormones, atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP), are attractive markers to reflect the pathophysiological conditions of heart diseases. ANP in response to load of the atrium and BNP in response to load of the ventricle are secreted from atrial and ventricular cardiomyocytes, and are responsible for the regulation of body fluid homeostasis and blood pressure. In human congestive heart failure (CHF), plasma ANP and BNP levels increase in relation to the deterioration of the clinical signs, elevated atrial and ventricular pressures, and left ventricular dysfunction. ANP and BNP are therefore suggested to be indicators for the severity, the therapeutic efficacy and the prognosis of human cardiac diseases.

ANP and BNP are thought to be useful in veterinary medicine similar to human medicine, but there are limited reports describing canine ANP. Therefore, the objectives of the present

study were to investigate the pathophysiological significance of canine ANP and BNP and to assess the clinico-pathological usefulness of canine ANP and BNP.

1. Tissue distributions of ANP and BNP in healthy dogs.

Complementary DNA (cDNA) clonings of canine ANP and BNP were first carried out, and mRNA expressions of ANP and BNP were investigated in canine various tissues using RT-PCR and Northern blot analysis for the purpose of determining of tissue distributions of canine ANP and BNP.

The lengths of cDNA and amino acid sequence of canine prepro-BNP were 420 bp and 140 residues, respectively. The length of amino acid sequence of canine prepro-BNP was the longest among those of mammals so far determined. The homology of amino acid sequence between canine and the other mammalian prepro-BNP was lower in comparison with prepro-ANP.

Secondly, mRNA expression of canine ANP was detected in atrium, ventricle, central nervous system and kidney, and abundant amount of BNP mRNA was detected in the atrium. On the other hand, mRNA expression of canine BNP was detectable only in atrium, but not the ventricle and central nervous system. Thus, both ANP