INFORMATION

Hokkaido University confered the degree of Doctor of Philosophy (Ph. D) in Veterinary Medicine on June 28 and September 25, 2002 to 3 recipients.

The titles of theses and other information are as follows :

Role of the 5-hydroxytryptamine$_3$ receptor in the regulation of lower gastrointestinal function : A study mainly using novel 5-HT$_3$ receptor agonist

Tetsuo Kiso

Neuroscience Research, Pharmacology Laboratories,
Institute for Drug Discovery Research,
Yamanouchi Pharmaceutical Co. Ltd.,
21 Miyukigaoka, Tsukuba, Ibaraki 305-8585, Japan

In the present study, effects of novel 5-HT$_3$ receptor agonist YM-31636 were mainly investigated to make clear the role of 5-HT$_3$ receptors in the regulation of lower gastrointestinal function. The possibility that selective 5-HT$_3$ receptor agonists would be an effective agent against gastrointestinal disorders is also investigated.

1) YM-31636 showed potent and selective affinity to 5-HT$_3$ receptors in ligand-binding experiments. This compound was almost full agonist in inducing contraction of guinea pig distal colon but partial agonist in positive chronotropic effect in guinea pig right atria. These results suggest that the different types of 5-HT$_3$ receptor exist in the distal colon and right atria of guinea pig.

2) YM-31636 facilitated defecation, without inducing diarrhea or emetic episode in ferrets. In addition, this agonist showed early and reliable onset of action compared to the existing laxatives. These results suggest that YM-31636 could be promising as an agent against constipation, and that the different types of 5-HT$_3$ receptor exist in the colonic neuron involving defecation and vagus nerve involving emesis.

3) YM-31636 restored atonic and spastic constipation in the ferret. It is concluded that selective 5-HT$_3$ receptor agonists could be promising as an agent against constipation.

4) Ramosetron, a selective 5-HT$_3$ receptor antagonist, prolonged the interval of migrating motor complex specifically in the stomach of unfed ferret. YM-31636 evoked giant migrating contraction (GMC)-like contractions in the colon, although it slightly influences basal gut motility pattern. These results suggest that the 5-HT$_3$ receptor plays important roles in the induction of GMC in the colon and in the occurrence of migrating motor complex in the stomach of unfed ferret.

5) 5-HT increased short-circuit current (I_{sc}) through the 5-HT$_3$ and 5-HT$_4$ receptors, and the response mediated by 5-HT$_4$ receptors was predominant in rat distal colon. In guinea pig distal colon, relatively larger I_{sc} response via the 5-HT$_3$ receptor was observed. YM-31636 weakly stimulated the I_{sc} in both guinea pigs and rats. These results suggest that this compound weakly stimulates water secretion to the extent of not causing diarrhea.

6) The effect of YM-31636 in the rat visceral pain models was examined. YM-31636

neither increased the magnitude of pressor response to colonic distension in anesthetized rats nor decreased the visceromotor threshold to colorectal distension in conscious rats. These results suggest that the selective 5-HT_3 receptor agonist facilitates defecation without increasing visceral pain in rats.

In conclusion, it is indicated that 5-HT_3 receptors play roles in the induction of GMC, in the facilitation of defecation and in the increasing of colonic secretion of water and electrolytes. Moreover, it is indicated that YM-31636 is a 5-HT_3 receptor agonist that selectively stimulates colonic motility, and thus could be promising as an agent against constipation, because it facilitates defecation or improves constipation without inducing emetic episodes, diarrhea and visceral pain. It is also suggested that the different types of 5-HT_3 receptor exist in the same species.

Original papers of this thesis appeared in *Eur. J. Pharmacol.*, 320 : 187-192 (1997), *Life Sci.*, 66 : PL 331-338 (2000), *Eur. J. Pharmacol.*, 409 : 195-201 (2000), *Eur. J. Pharmacol.*, 424 : 151-157 (2001) and *Eur. J. Pharmacol.*, 431 : 35-41 (2001)

Molecular cloning and characterization of antigens recognized by monoclonal antibodies targeting tumor endothelial cells

Kenji Taniguchi

Pharmaceutical Research Laboratory II
Chugai Pharmaceutical Co., Ltd.
Gotemba 412-8513, Japan

Solid tumors get nutritions and oxygen from the host blood supply and form new capillary vessels when the size exceeds 2 mm diameter. Chemotherapy shows cytotoxic effects to both tumor cells and highly proliferative normal tissues like bone marrow and intestine. Chemotherapy has to meet "total cell killing" of tumor cells to cure cancer patients. It is, however, very difficult for chemotherapeutic agents to reach all tumor cells in solid tumors, because tumor vessels do not run uniformly in solid tumors. Due to its low specificity and accessibility to tumor cells, chemotherapy can, thus far, hardly cure the patients of solid tumors. In contrast to its poor curability of solid tumors, the usefulness of targeting tumor vessels has been highlighted. Systemically administered agents targeting tumor vessels may block blood supply and inhibit proliferation of surrounding tumor cells effectively.

Monoclonal antibodies (MAbs) had been generated against cultured tumor endothelial cells (TEC) separated from rat KMT-17 solid tumors and antigens of 40 kD and 80 kD were recognized by a series of the MAbs. Also, TES-23 MAb had shown anti-tumor effects on KMT-17 solid tumors and stained tumor vessels of human cancer tissues.

In the present study, molecular cloning and characterization of 40 kD and 80 kD antigens were conducted and the cross-reactivity of TES-23 MAb to human antigen was examined based on the possibility of its clinical use. Firstly, the 80 kD antigen, which was also expressed on ROS-17/2.8-5 rat osteosarcoma cells, was identified as rat hematopoietic CD 44 (CD44 H) by panning screening of cDNA li-