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INVITED LECTURES

Diseases of enteric peptidergic neurons

Yuan-Fang Chen

Yuan-Fang Chen, MD, Peking Union Medical College, Beijing, China

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THE ENTERIC NERVOUS SYSTEM (ENS)

ENS is the part of intrinsic nervous system that is embedded in the walls as myenteric or submucosal ganglia throughout the gastrointestinal tract. It plays an important part in controlling or modulating all the digestive functions, including motility, secretion, absorption, ion transport, blood flow, hormone release, *etc*. Although ENS is modulated by extrinsic autonomic nerves (vagal and sympathetic), it is characteristically able to act autonomously, *i.e.*, independently of CNS, hence the name "minibrain" of the GI tract.

The great majority of enteric neurons are peptidergic, comprising 80% of total myenteric neurons and 85% of total submucosal neurons in the guinea pigs[1]. These peptidergic neurons may contain one or more neuropeptides, which act in concert with classic transmitters (cholinergic or adrenergic) or other transmitters (GABA, amines, ATP, purines). Co-localization of neuropeptides and other transmitters can usually be observed in the same enteric neuron. The peptidergic neurons are the major non-cholinergic, non-adrenergic (NANC) nerve cell populations in the GI tract.

Sphincters of the GI tract play an important role in coordinating GI motility. A number of peptides and peptidergic neurons are involved in the regulation or modulation of sphincter functions, such as vasoactive intestinal peptide (VIP), substance P (SP), opioids, galanin, neuropeptide Y (NPY), and calcitonin gene-related peptide (cGRP). Abnormality in the number of peptidergic neurons or peptide content may result in GI motor diseases[2].

Deficit or dysplasia of enteric neurons may also lead to a variety of gastrointestinal motor diseases.

ACHALASIA

Achalasia is an esophageal disease characterized by incomplete relaxation of lower esophageal sphincter (LES) and incomplete distal esophageal peristalsis, resulting in dysphagia and dilatation of the esophagus. Recent immunohistochemic al studies of human esophagus revealed that the LES receives terminations positive for VIP (in 96%), cGRP (in 80%), and galanin (in 59%), and that 55% myenteric neurons are nitrinergic[3]. VIP and cGRP induce relaxation or decrease the tone of LES, whereas SP and galanin induce contraction or increase the tone of LES. VIP also reduces the increase in LES pressure stimulated by gastrin[4]. In patients with achalasia, VIP and VIP-containing fiber s in LES specimens are markedly decreased or virtually lacking[2], Transcutaneous electrical nerve stimulation decreases LES pressure in achalasia and in the meantime enhances systemic VIP concentration. Regardless of the above findings, the role of VIP in the pathogenesis of achalasia is still being questioned[5].

CONGENITAL ESOPHAGEAL STENOSIS (CES)

CES is a rare disease with narrowed esophageal lumen, aperistalsis and dysphagia since childhood. A marked reduction in myenteric nitrergic nerves was observed without significant quantitative changes in VIP, SP, and galanin neurons[6].

INFANTILE PYLORIC STENOSIS

This is an inborn disorder characterized by lack of relaxation in the pyloris, presented as refractory vomiting soon after birth. Normally, VIP and galanin induce relaxation or decrease the tone of the sphincter of pylorus whereas SP and opioids induce contraction or increase the tone of the sphincter of pylorus. Immunohistochemically, peptidergic ganglia or nerve fibers can be observed in the pylorus. In this disease, however, immunoreactive VIP, SP, NPY, and enkephalin nerve fibers are lost or decreased in the pylorus[2].

HIRSCHSPRUNG'S DISEASE

Hirschsprung's disease (aganglionosis coli) is characterized by segmental aganglionosis and lack of relaxation of diseased colon, with aperistalsis and dilatation of colon proximal to the diseased segment. Clinically, it is presented as refractory constipation. Hypoganglionosis and neuronal dysplasia of colon are related diseases with similar symtoms. Normally, peptidergic as well as nitrinergic neurons are present in human myenteric and submucosal ganglia, in Hirschsprung's disease, normal populations of neural cell bodies were observed only in 20% of patients, and immunohistochemical studies have revealed the absence of NANC inhibitory innervation. Neuropeptide immunoreactive nerve fibers, such as VIP, pituitary adenylate cyclase-activating peptide (PACAP), gastrin-releasing peptide (GRP), cGRP, SP, enkephalins, and galanin, are all reduced in number. In contrast, the cholinergic and adrenergic innervations are increased in the aganglionic segment. Notably, NPY nerve fibers are also increased in number, probably reflecting the adrenergic hyper-

innervation. Nitric oxide synthetase (NOS) is almost absent in the diseased segment[7,8].

CONSTIPATION WITH HYPERGANGLIONOSIS

This is a disease in young children presented as severe constipation and hyperplastic ganglia throughout the large and small intestines. Immunohistochemical study shows lowered expression of cGRP[9].

IDIOPATHIC CHRONIC CONSTIPATION (ICC)

Low total neuron density was observed at the myenteric plexus in patients with ICC. Using anti-VIP and anti-NOS antibodies, it can be found that the density of VIP-positive neurons is low while that of NOS-positive neurons is high in both myenteric and submucosal plexuses. These data support the postulation that in addition to the decrease in VIP neurons, the excessive production of NO may cause the persistent inhibition of intestinal contractions in ICC[10].

DIABETIC ENTERONEUROPATHY

Using the technique of *in situ* hybridization, it was shown that VIP mRNA con tent in myenteric neurons is significantly higher in streptozotocin-induced diabetic rat than in the controls, although the number of cell bodies is lower in diabetic rats compared to controls[11].

CHAGAS DISEASE

Chagas disease is characterized by the ganglionic damage in gastrointestinal smooth muscles and other muscles due to infestation with Trypanosoma cruzi in la tin America. Furthermore, the toxin released by the parasite is believed to be responsible for the damage and ablation of myenteric ganglionic neurons, which eventually lead to motor dysfunction, megaesophagus, and megacolon. VIP and SP neurons are decreased in Chagas disease[12].

REFERENCES

1 **Gershon MD**, Kirchgessner AL, Wade PR. Functional anatomy of the enteric nervous system. In Johnson LR (ed): Physiology of the Gastrointestinal Tract, 3rd, editor. *Raven Press, New York*, 1993; **1**: 381

2 **DeVault K**, Rattan S. Physiological role of neuropeptides in the gastrointestinal smooth muscle sphincters: neuropeptides and VIP nitric oxide interactions. In Walsh JH, Dockray GJ (eds). Gut Peptides. Raven Press, New York, 1995: 715

3 **Singaram C**, Sengupta A, Sweet MA, Sugarbaker DJ, Goyal RK. Nitrinergic and peptidergic innervation of the human oesophagus. *Gut* 1994; **35**: 1690-1696 [PMID: 7530228 DOI: 10.1136/gut.35.12.1690]

4 **Tangoku A**, Murakami T, Ozasa H, Honma K, Suzuki T. Role of VIP on achalasia of the esophagus. *Biomed Res* 1992; **13** Suppl 2: 289

5 **Mao YK**, Wang YF, Daniel EE. Distribution and characterization of vasoactive intestinal polypeptide binding in canine lower esophageal sphincter. *Gastroenterology* 1993; **105**: 1370-1377 [PMID: 8224641 DOI: 10.1016/0016-5085(93)90141-X]

6 **Singaram C**, Sweet MA, Gaumnitz EA, Cameron AJ, Camilleri M. Peptidergic and nitrinergic denervation in congenital esophageal stenosis. *Gastroenterology* 1995; **109**: 275-281 [PMID: 7541000 DOI: 10.1016/0016-5085(95)90294-5]

7 **Tomita R**, Munakata K, Kurosu Y. Peptidergic nerves in Hirschsprung's disease and its allied disorders. *Eur J Pediatr Surg* 1994; **4**: 346-351 [PMID: 7538322 DOI: 10.1055/s-2008-1066132]

8 **Larsson LT**. Hirschsprung's disease--immunohistochemical findings. *Histol Histopathol* 1994; **9**: 615-629 [PMID: 7981507]

9 **Gittes GK**, Kim J, Yu G, de Lorimier AA. Severe constipation with diffuse intestinal myenteric hyperganglionosis. *J Pediatr Surg* 1993; **28**: 1630-1632 [PMID: 7507990 DOI: 10.1016/0022-3468(93)90124-4]

10 **Cortesini C**, Cianchi F, Infantino A, Lise M. Nitric oxide synthase and VIP distribution in enteric nervous system in idiopathic chronic constipation. *Dig Dis Sci* 1995; **40**: 2450-2455 [PMID: 7587830 DOI: 10.1007/BF02063253]

11 **Belai A**, Facer P, Bishop A, Polak JM, Burnstock G. Effect of streptozotocin-diabetes on the level of VIP mRNA in myenteric neurones. *Neuroreport* 1993; **4**: 291-294 [PMID: 8477051 DOI: 10.1097/00001756-199303000-00016]

12 **Long RG**, Bishop AE, Barnes AJ, Albuquerque RH, O'Shaughnessy DJ, McGregor GP, Bannister R, Polak JM, Bloom SR. Neural and hormonal peptides in rectal biopsy specimens from patients with Chagas' disease and chronic autonomic failure. *Lancet* 1980; **1**: 559-562 [PMID: 6153742 DOI: 10.1016/S0140-6736(80)91054-5]

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