THE PAMCREATIC-POLYPEPTIDE FAMILY OF PEPTIDES: THEIR ROLE IN THE BRAIN-GUT AXIS

Joseph S. Davison
Department of Physiology and Biophysics, Faculty of Medicine, University of Calgary, Calgary, Alberta, Canada

• In this volume of *Biomedical Reviews,* Rogers and Hermann (1) present an interesting model for the regulation of gastrointestinal function by two peptides, neuropeptide Y (NPY), and peptide YY (PYY), both of which belong to a related group of peptides known as the pancreatic polypeptide (PP)-fold family of peptides. In this review, largely of their own innovative work, they develop the hypothesis that PYY, acting as a humoral (hormonal) agent, may be a maj or inhibitory factor in the regulation of the upper gastrointestinal tract. In contrast, NPY would appear to be a maj or excitatory transmitter. How can two structurally homologous peptides produce such divergent actions?

The explanation proposed in this review is that PYY is released from within the gastrointestinal tract, but exerts its effects through an action on the dorsal vagal complex (DVC), which consists of the dorsal vagal nucleus, the nucleus of the tractus solitarius (NTS), the area postrema (AP), and other subnuclei. In this area, PYY acts preferentially on Y2 receptors leading to inhibition of gastrointestinal activity. In contrast, it is proposed that NPY is released from nerve terminals within the DVC, and acts preferentially on Y1 receptors leading to excitation of the upper gastrointestinal tract. This hypothesis is discussed in the light of a recent observation that PYY released from the ileum is rapidly cleaved by a diaminopeptidase (DAP-IV) to produce a fragment (PYY 13-36) that is a potent and specific Y2 agonist

Corespondence to Dr Joseph S. Davison, Department ofPhysiology and Biophysics, The Faculty of Medicine, The University of Calgary, 3330 Hospital Drive NW, Calgary, Alberta, CanadaT2N4N1. Tel: 1 (403) 2206 031, Fax: 1 (403) 2834 740, E-mail: 28551 (gaoss.ucalgary.ca

(2). Thus, two structurally related peptides with similar biological activity profiles can exert totally divergent physiological effects, based on their relative affinities for distinct receptor subtypes and on their different sites of release, and therefore have a different route whereby they are able to modify the activity of neurons within the DVC.

While the evidence compiled by these authors strongly supports this attractive hypothesis, further proof is required as they themselves admit. In particular, they draw attention to a perceived need for a histoanatomical demonstration that Yl and Y2 receptors are located on different components of the DVC, and for aneurophysiological verification of this. Implicit in this suggestion is the assumption that different populations of DVC neurons are responsible for excitation and inhibition of gastrointestinal activity. This is undoubtedly so, but does excitation or inhibition within the gastrointestinal tract depend solely upon activation of these two distinct pathways? Probably not.

Neurophysiological studies of the DVC based on micro-electrode recordings from the NTS or recording from single vagal efferent fibres (3) have revealed that DVC neurons are usually tonically active and may be excited or inhibited by any specific sensory input. Therefore, it seems probable that excitation or inhibition within the gastrointestinal tract may not only depend upon activation of the appropriate descending excitatory or inhibitory pathway, but perhaps may depend also on reciprocal inhibition of the opposing pathway (4). Should histological studies reveal a differential distribution of Yl and Y2 receptors on neurochemically distinct DVC neurones, this

would, of course, strongly support the authors' hypothesis and, moreover, would suggest that the different physiological effects of NPY and PYY are due to their ability to activate different descending vagal pathways. However, the existence of Yl and Y2 receptors on the same neurons does not invalidate the central hypothesis since the receptors could be linked to a different intracellular messenger system leading to either excitation or inhibition of the DVC neurons. In many ways, a neurophysiological analysis of the actions of highly selective Y1 and Y2 agonists and antagonists would provide the most definitive proof of the hypothesis.

One of the intriguing concepts underlying this hypothesis is the notion of humoral regulation of central nervous system function. This is not aunique concept, since similar mechanisms have been proposed for the regulation of gastrointestinal and other autonomic functions as well as for the regulation of complex behaviours, such as food and water intake, emesis, fever, etc. However, in all these cases, including the mechanism proposed by Rogers and Hermann (1), a major question that needs to be addressed is how does the humoral agent communicate with the CNS neurons? Does it act peripherally to stimulate primary afferent nerves? Does it cross the blood-brain barrier or act within the cerebroventricular system on receptors located at the site of circumventricular organs? All three of the above possibilities could explain the actions of putative hormonal modulators of neural function.

For example, several studies have shown that circulating peptides such as cholecystokinin can activate vagal sensory fibres in the muscle wall of the stomach (5) or the mucosa of the small intestine (6) by a direct action on the nerve endings. This leads to activation of certain areas of the caudal brain stem and hypomalamus as revealed by *fos* immunohistochemistry (7). Certain emetic substances are believed to act on a chemoreceptor trigger zone within the DVC, either by crossing the blood-brain barrier or by acting on cells lining the wall of the fourth ventricle. Recently, we have shown that a peripherally acting emetic stimulus (hypertonic saline infused into the duodenum) activates/os expression in parts of the DVC (NTS, AP) (8). Most of this *fos* expression is abolished by combined abdominal vagotomy and splanchnotomy (9). However, a significant level *of fos* expression persists in the activator protein-1 after the afferent sensory pathways between the intestine and brain stem have been severed implying a humoral or hormonal effect at the level of AP.

Another aspect of the central actions of the PP-fold family of peptides which can lead to divergent effects on the gastrointestinal motility is their widespread distribution within the brain, in particular NPY, which is one of the most ubiquitous of the neuropeptides in the mammalian brain. The highest NPY concentration in the rat is found in the hypothalamus. The parvocellular division of the paraventricular nucleus (PVN) of the hypothalamus is particularly densely innervated by NPY-containing nerve terminals and fibres (10). We have shown that microinjection of NPY into the PVN can both inhibit and excite gastric acid secretion and motility depending upon the precise site of injection (11). The more rostral portions of the PVN appear to cause activation of a descending pathway to the DVC that stimulates vagal excitatory pathways to the stomach (12). In more caudal regions, NPY activates a descending pathway which in turn activates the intermediolateral column, leading to increased sympathetic activity and suppression of cholinergic tone through activation of a-adrenoceptors on intrinsic neurons (13). Thus, even one and the same peptide can exert opposing effects depending up on its precise locus of action. So far, we have only studied the receptor subtype involved in relation to the excitatory effects of NPY in the PVN, and have found, as Rogers and Hermann (1) describe for the DVC, that it appears to activate a Yl receptor subtype. In contrast to the situation in the DVC, the Y2 agonist (NPY 13-36) had no effect on secretion or motility (12). We do not know yet whether the inhibitory effects of NPY in the caudal PVN are due to activation of a different receptor subtype.

We have also reported various effects of PP, PYY, and NPY on duodenal and colonic motility and gastric secretion acting at sites within the thoracic spinal cord (14-16). During these studies, we rarely saw evidence of antagonist effect of NPY and PYY but this may have been due to the experimental conditions in that we did not use an experimental model of stimulated gastrointestinal activity as did Rogers and Hermann (1). Interestingly, however, we frequently observed biphasic responses (e.g. inhibition followed by excitation) with PYY.

In summary, Rogers and Hermann provide an intriguing hypothesis to explain the antagonistic effects on gastric function of two closely related peptides acting within the DVC. In this *Editorial Comment,* I have attempted to identify some of the more important questions still to be addressed, and to suggest that similar studies are required in other areas of the CNS involved in the regulation of gastrointestinal function, most notably the hypothalamus (in particular the PVN), and the spinal cord.

REFERENCES

1. Rogers RC, Hermann GE. Peptide YY and neuropeptide Y: reciprocal control of digestion *via* modulation of the brain-gut axis. *Biomed Rev* 1997; 8: 55-69

2. Grandt D, Dahms P, Shimiczek M, Eysselein VE, Reeve JR, Mentlein R. Proteolytic processing by dipeptidyl amino peptidase IV generates receptor selectivity for

peptide YY [PYY]. *MedKlinik* 1993; 88: 143-145.

3. Davison JS, GrundyD. Modulation of single vagal efferent fibre discharge by gastrointestinal afferents int he rat. *J Physiol* 1978; 284: 69-82.

4. Davison JS. Central organization of gastrointestinal vagal reflexes. *Mod Concepts Gastroenterol* 1992; 3: 129-144.

5. Davison JS, Clarke GD. Mechanical properties and sensitivity to CCK of vagal, gastric, slowly adapting mechano-receptors. *Am J Physiol* 1988; 255: G55-G61.

6. Richards W, HillsleyK, EastwoodC, GrundyD. Sensitivity of mucosal afferents to cholecystokinin and its role in afferent signal transduction in the rat. *J Physiol* 1996; 497: 473-481. . •• . - ; • , • ; . • ; - • > . . ; • , - > : - • - - . • • • . - . • : • -

1. Eraser KA, Davison JS. Cholecystokinin-induced *c-fos* expression in the rat brain stem is influenced by vagal nerve integrity. *Exp Physiol* 1992; 77: 225-228.

8. Boissonade FM, Sharkey KA, Davison JS. For expression in ferret dorsal vagal complex after peripheral emetic stimuli. *Am J Physiol* 1994; 226: Rl 118-1126.

9. Boissonade FM, Davison JS. Effect of vagal and splanchnic nerve section on Fos expression in ferret brain stem after emetic stimuli. *Am J Physiol* 1996; 271: R228-R235. .

10. Bai FL, Yamano M, Shiotani Y, Emson PC, Smith AD, Powell JF *et al.* An arcuato-paraventricular and dorsomedial hypothalamic neuropeptide Y-containing system which lacks noradrenaline in the rat. *Brain Res* 1985; 331: 172-175.

11. Humphreys GA, Davison JS, Veale WL. Injection of neuropeptide Y into the paraventricular nucleus of the hypothalamus inhibits gastric acid secretion in the rat. . . *Brain Res* 1988; 456: 241-248.

12. Davison JS, Pearce CM. Actions of intrahypothalamic NPY on gastric function. *Proc West Pharmacol* 1997; 40: 135-136.

13. Humphreys GA, Davison JS, Veale WL. Hypothalamic neuropeptide Y inhibits gastric acid output in rat: role of ;; the autonomic nervous system. *Am J Physiol* 1992; 263: G726-G732.

14. Wager-Pag, SA, Ghazali B, Anderson W, Veale WL, Davison JS. Neuropeptide Y, peptide YY and pancreatic polypeptide modulate duodenal and colonic motility at a thoracic spinal site in rats. *Peptides* 1992; 13: 807-813.

15. Wager-Pag, SA,RaizadaE,VealeWL,DavisonJS.Spinal modulation of duodenal and colonic motility and arterial blood pressure by neuropeptide Y, neuropeptide Y fragment 13-36, peptide YY and pancreatic polypeptide in rats: involvement of the cholinergic nervous system. *Canad J Physiol Pharmacol* 1993; 7: 112-119.

16. Wager-Pag, SA, Rosenbaum G, Veale WL, Davison JS. Spinal and peripheral modulation of gastric acid secretion and arterial pressure by neuropeptide Y, peptide YY, and pancreatic polypeptide in rats. *Peptides* 1993; 14: 1299-1308.