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PEPTIDE YY AND NEUROPEPTIDE Y: RECIPROCAL CONTROL OF DIGESTION *VIA* MODULATION OF THE BRAIN-GUT AXIS

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SUMMARY

• *Peptide tyrosine-tyrosine (PYY) and neuropeptide tyrosine (NPY) are emerging as potent central nervous system regulators of digestive functions. There is, however, considerable debate concerning the mechanisms and even the direction of autonomic effects mediated by these peptides. PYY is thought to be the hormonal "enterogastrone" released by the ileum after feeding. This peptide acts on vagal reflex control circuits in the dorsal vagal complex (DVC) of the medulla oblongata to reduce gastric motility, i.e. the "Heal brake". However, equally convincing evidence is available to suggest that PYY and its close structural relative NPY may also act in the DVC to increase gastric motility through vagal mechanisms. This activation effect, particularly of NPY, has been linked to the increase in digestive functions seen at the onset of feeding behaviour, i.e. Pavlov's "cephalic phase". We hypothesize that the confounding observations produced by these peptides are due to agonist effects on two different receptor types referred to as Yl and Y2. Both receptors are present in the DVC but may be accessed differentially by peripheral humoral (PYY) versus central neurotransmitter (NPY) pathways. Our experiments show that the hormonal effect of PYY to suppress gastric functions such as the "Heal brake" is consistent with the activation of the Y2 receptor in the DVC, while NPY-ergic effects to increase gastric functions are mediated by the Yl receptor. These results are corroborated by neurophysiological studies of the effects ofYl and Y2 agonist peptides on single vagal efferent neurons. The seemingly paradoxical effects of PYY and NPY on the central neural control of gastric motility are reviewed in terms of the possible differential localization of Yl versus Y2 receptors within the DVC. Specific reference is also made to recent observations that PYY is rapidly converted to a Y2 agonist by an ubiquitous dipeptidyl aminopeptidase.* ***(Biomed Rev 1997; 8: 55-69)***

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INTRODUCTION

• PYY and NPY were originally extracted and purified from porcine small intestine and brain, respectively (1-5). Both contain 36 amino acids, show a 70% sequence homology and display a high degree of three dimensional structural conservation (3, 5). PYY-releasing endocrine cells are located mainly in the mucosa of the terminal ileum and colon (4-

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In contrast, NPY is one of the most abundant peptides found in neurons in the brain. It is concentrated in neural pathways associated with the control of feeding behaviour, endocrine and autonomic functions. Its synthesis and release are strongly associated with physiological conditions leading to increased food intake such as growth, pregnancy, and starvation. NPY injections into hypothalamic and brainstem structures associated with the control of feeding behaviour elicit dramatic

elevations in feeding (11-15).

PYY EFFECTS ON DIGESTIVE PROCESSES

• Following a meal, PYY levels in plasma are increased significantly and remain elevated for several hours (4, 5). Circulating PYY concentrations can also be specifically elevated in response to direct infusion of oleate into the ileum (5, 6, 10). PYY produces inhibitory effects on digestive functions, gastric acid output, motility, and emptying as well as reduction of stimulated pancreatic exocrine secretion, and a prolongation of intestinal transit time (4, 5, 7, 8, 16-18). All of these effects are dependent upon intact vagal connections between the brainstem and the digestive tract (5).

DORSAL VAGAL COMPLEX: CENTRAL NERVOUS SYSTEM TARGET FOR THE HORMONAL ACTION OF PYY

• The dorsal vagal complex of the medulla oblongata (DVC) contains the basic neuronal circuitry for the reflex vagal control of digestion, often termed the vago-vagal reflexes. Vago-vagal reflex control is mediated by general visceral afferent fibers in the vagus nerve which carry a wide variety of sensory information from the gut. These vagal afferent fibers synapse in the nucleus of the solitary tract (NST). This nucleus maintains connections with vagal motorneurons in the dorsal motor nucleus of the vagus (DMN), which are the source of virtually all parasympathetic innerva-tion of the subdiaphragmatic viscera (19). The NST is also the source of input to interneurons in the reticular formation which control, by descending pathways, sympathetic efferent activity in preganglionic neurons of the intermediolateral cell column (20). Additionally, the NST is the principal source of ascending visceral afferent information used by other central nervous system (CNS) structures to monitor a wide variety of physiological parameters including, but certainly not limited to, the progress of digestion of a meal.

Several categories of vago-vagal reflexes have been identified. The simplest such reflex is the gastric accommodation reflex, which utilizes mucosal contact receptors in the antrum to control the parasympathetic "tone" of the proximal stomach, and the rate of delivery of chyme to the duodenum. Evidence suggests that this is a simple disynaptic reflex whereby activation of vagal afferents activates NST neurons which, in turn, inhibit excitatory cholinergic neurons in the DMN (21,22). Other vago-vagal reflex "types" may be much more complicated. The gastric receptive relaxation reflex which is elicited by the activation of esophageal distension sensors during swallowing serves as an example. This reflex may involve the simultaneous and coordinated inhibition of DMN neurons controlling cholinergic excitation of the stomach and excitation of DMN neurons controlling the inhibitory non-adrenergic, non-cholinergic (NANC) enteric inputs to gastric smooth muscle (23). The -end result is the relaxation of the proximal stomach to accept ingesta.

Evidence has accumulated over the last few years which suggests that this brainstem region, which contains the digestive tract reflex control circuits, i.e. the DVC, may be outside the confines of the "blood-brain barrier" (24-26). Therefore, vago-vagal reflex circuitry in the brainstem may also be under "humoral afferent control" (20). The best example for such "endoneurocrine" regulation of autonomic functions may be found in the explanation of the gastroinhibitory effects of PYY.

Saturable and specific binding of circulating PYY to sites in the DVC has been demonstrated (26). This suggests that circulating PYY is capable of exerting direct feedback control ove* th/e progress of digestion by actmg OTI vago-vagal reflex, control circuitry. Our earlier physiological studies showed that microinjection of low doses (4-400 fmol in 20 nL) of PYY into the DVC could produce a vagally-mediated suppression of stimulated gastric motility (27). On the basis of this evidence, we suggested that PYY could be responsible for an "ileal brake" effect on gastric motility. In other words, ileal filling induces a negative feedback suppression of further gastric transit via PYY release. Circulating PYY then acts directly on vagal regulatory circuits in the brainstem to control gastric function (20). However, relatively higher doses of PYY (greater than 4 pmol in 20 nL) applied to the same brainstem area, i.e. the DVC, can also strongly activate gastric functions (27, 28). This dichotomy of CNS effects is also elicited by NPY. Thus, many reports link the release of NPY with the augmentation of motility (and other gastrointestinal functions) during the "cephalic phase" of digestion associated with food intake (29-32). Others, however, find that NPY injected centrally reduces digestive functions possibly *via* action on the same circuitry (33-35). One explanation for the apparent paradoxical experimental effects of NPY and PYY may have to do with the existence of multiple receptor populations for these peptides which overlap in the DVC.

Binding sites for both PYY and NPY have been identified in the peripheral tissues and in the CNS. For example, PYY receptors have been found along the gastrointestinal tract as well as pancreas, spleen, kidney tubules, and several neuroendocrine cell lines (1, 36-41). In the brain, NPY and PYY binding sites are seen in a variety of areas, including cortex, hypothalamus, pons and, especially, the medulla oblongata (11, 15, 23). Results from binding studies have characterized at least five distinct subtypes of receptors for NPY and PYY, denoted Yl through Y5. Two of these receptors subtypes, Yl and Y2, are both found in large quantities in the dorsal vagal complex of the medulla. Both Y1 and Y2 receptors bind PYY

and NPY with high affinity (42). The Y2 subtype can be activated by C-terminal fragments of PYY and NPY, while the Yl subtype requires a full sequence of either polypeptide (13, 42). The DVC area containing Yl and Y2 receptors receives an especially dense NPYergic terminal innervation (11, 43). Additionally, a specific receptor for the structurally similar pancreatic polypeptide (PP) has been described (13, 15, 44-47). Therefore, the overlapping distribution of Yl and Y2 receptors in the DVC may explain some of the confusion concerning the physiological role of PYY and NPY to modulate vago-vagal reflex control of gastric motility. To test this idea, we investigated the effects of PYY, NPY, Y1, and Y2 agonists on gastric motility (measured by strain gauges) when microinjected directly into the DVC under conditions of either maximal central vagal stimulation of motility or in the basal, unstimulated state (12, 48, 49).

DVC ACTIONS OF PYY, NPY AND ANALOGS

• PYY is normally released following feeding behaviour when gastrointestinal motility is elevated (4-6,10). To model this motility state in the anesthetized rat, the peptide thyrotro-pin releasing hormone (TRH) is microinjected onto the DVC. This peptide, which is normally released from terminal endings of the raphe nuclei in the brainstem onto neurons of the DMN, promotes a specific excitation of parasympathetic vagal projections to the stomach thus mimicking the increase in gastric motility following feeding (20, 50-52).

Microinjection of the Y2 agonist (PYY 13-36) into the DVC (20 nL containing graded concentrations of the agonist peptides) causes a dose-dependent inhibition of TRH-stimulated antral motility as previously seen (27) after microinjection of the full sequence of PYY (Fig. 1). On the other hand, applica-

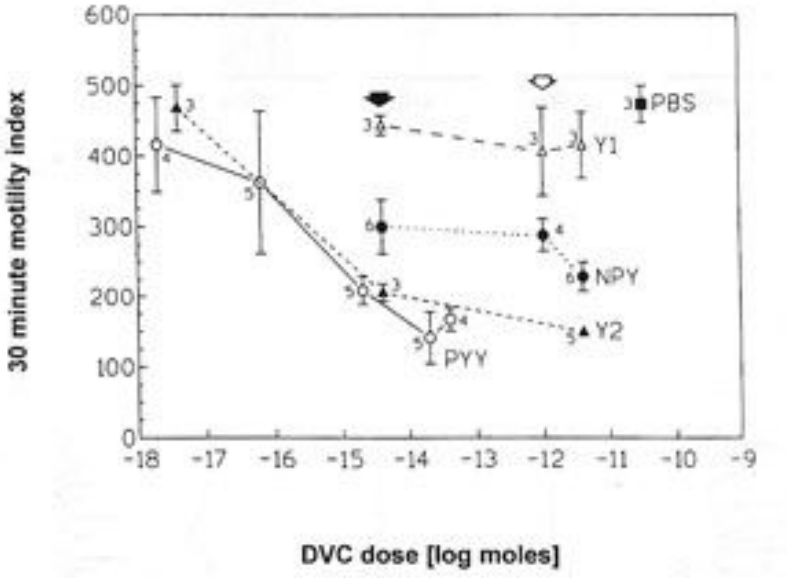

Figure 1. *Effects of different doses of PYY, NPY, Yl, and Y2 agonists microinjected into the dorsal vagal complex on TRH-stimulated gastric motility. Data are depicted as means, +/- standard error. Statistical comparisons made at the 4000 fmol dose (open arrow) reveal significant between-group differences. An ANOVA produced an* $F_{3}j_{3}$ *=36.2; P<0.001. Post-hoc Bonferroni comparisons between groups at the 4000 fmol dose indicate: PBS vs Yl, no significant difference; PBS vs NPY, P<0.001; PBS vs Y2, P<0.001; Yl vs NPY, P<0.001; Yl vs Y2, P<0.001; NPY vs Y2, no significant difference. Results are similar for the 4 fmol comparison (filled arrow). Here, an ANOVA produced an* $F_{3}.u$ *= 12.13; P<0.001. Post-hoc Bonferroni comparisons for 4 fmol yield: PBS vs Yl, no significant difference; PBS vs NPY, P<0.05; PBS vs Y2, P<0.01; Yl vs NPY, P<0.05; Yl vs Y2, P<0.01; NPY vs Y2, no significant difference. Numbers on graph indicate Nfor each*

tions of the Y1 agonist (LeuSl, Pro34 NPY) produced no apparent reduction in the TRH-stimulated increase of antral motility. Although application of the full sequence of NPY to the DVC inhibited motility more than Y1 agonist, the inhibition was not as potent as that produced by equal doses of PYY or Y2 agonist injections into the DVC. Figure 2 illustrates the

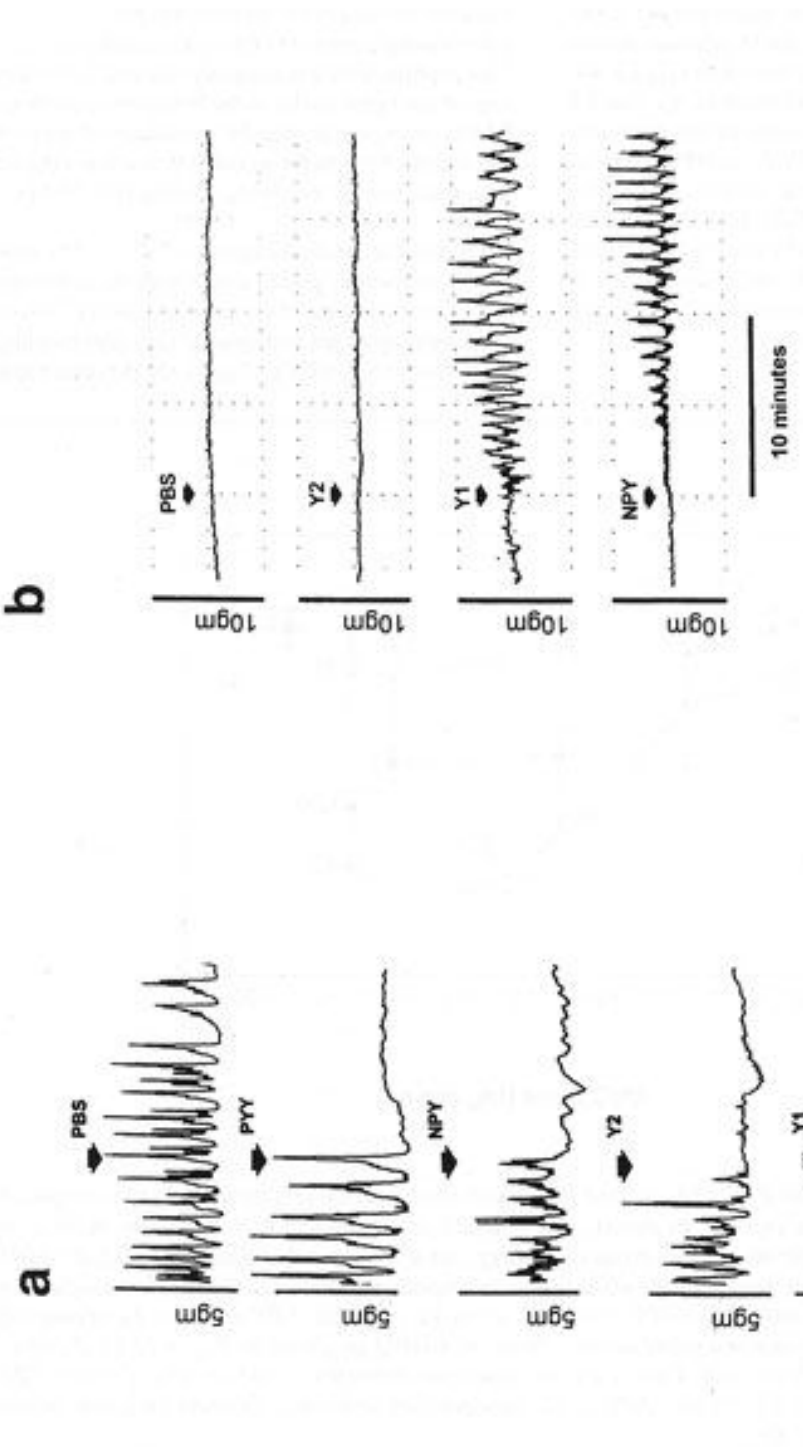

Figure 2. Polygraph records of the low dose inhibitory effects of PYY and its analogs on stimulated gastric motility (a). Effects of PYY, NPY, Y2, and Y1 agonists placed bilaterally in the DVC on central TRH-stimulated gastric motility. PBS (40nL) is injected at the arrow. All peptides were injected (arrows) at a dose of 40 fmol in 40nL. Polygraph records of the high dose excitatory effects of NPY and Y1 agonist on basal gastric motility (b). This dose of Y1 or NPY (4000 fmol) applied to the DVC typically elevates motility for approximately one hour. From Ref 48.

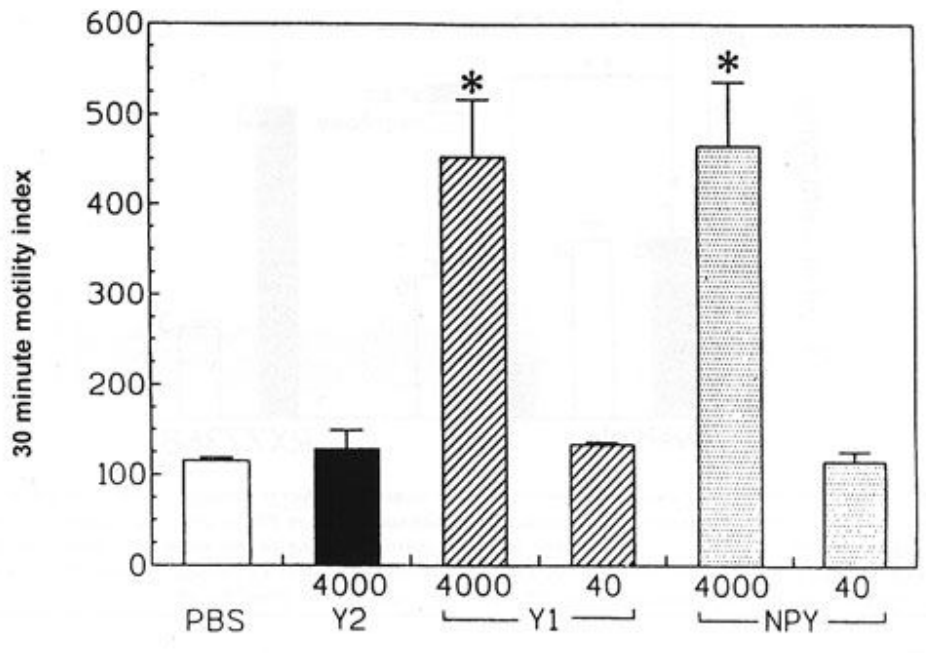

*Figure 3. Effects on basal gastric motility of NPY, Yl, or Y2 agonists microinjected into the dorsal vagal complex. Data are depicted as means, +/- standard error. * = Bonferroni comparison to PBS was significantly different at the P<0.01 level. Note that only high doses (4000 fmol) of either NPY or the Yl agonist elicited increases in gastric motility. From Ref 48.*

typical effects of all four peptides on strain-gauge recordings of gastric motility (48).

The results on motility are exactly reversed for the effects of NPY, Yl and Y2 analogs in the DVC on basal gastric motility: the Yl agonist and NPY strongly activated motility from the low, basal state, while the Y2 agonist produced no effect on the already low motility. Figure 3 shows the typical effects of these peptides on gastric motility when applied to the DVC under anesthesia. Obviously, the anesthetic state of the preparation may significantly alter the motility level of the rat, as well as bias the effects of centrally applied peptides. However, it has been observed recently that the intracisternal application of PYY in awake rats produces a dose-dependent inhibition of gastric motility which is vagally-mediated (Fig. 4) (49).

- **Neurophysiological Studies**

The effects of Yl and Y2 agonists on the excitability of vagal efferent neurons in the DMN show that these neurons may be an important target of the direct effects of PYY and NPY. Extracellular recording from spontaneously active DMN neurons, both *in vivo* and *in vitro,* confirm that PYY and the Y2 agonist peptide exert a predominantly inhibitory effect on DMN neurons. The inhibitory PYY and Y2 agonist effects on DMN neurons recorded *in vitro* under high magnesium/low calcium conditions ("synaptic blockade") are additionally significant, because they suggest that PYY effects on the DMN are direct and not mediated by synaptic inputs from other neurons. In contrast, similar studies done with the Yl agonist reveal that its effects on DMN neurons is excitatory (Figs 5-8) (53).

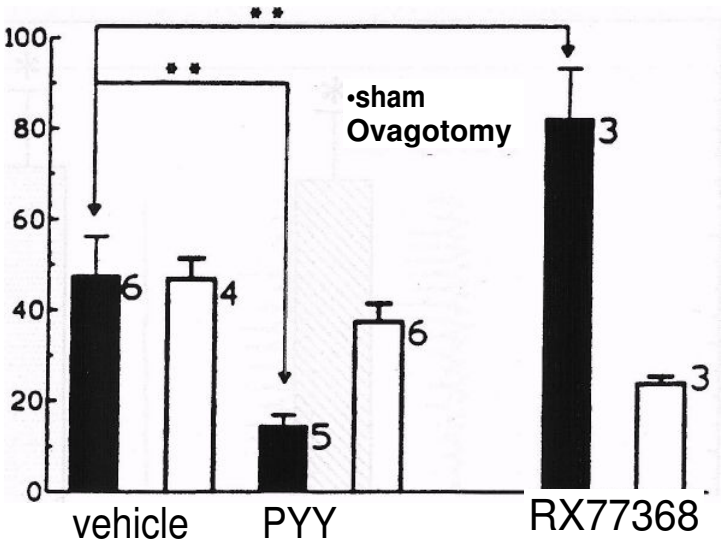

***Figure** 4. Intracisternal PYY in the awake rat suppresses gastric transit; the effect is mediated by the vagus nerve. Effects on gastric transit of intracisternal injections of vehicle (PBS), 400fmol of PYY in PBS or the TRH agonist RX77368 (33 pmol). Vagotomy does not effect basal, i.e. vehicle injection, gastric emptying in this model, but does eliminate the inhibitory effects of PYY as well as the excitatory effects of the TRH analog known to act via vagal efferents (REF). Numbers on graph indicate Nfor each experimental group. ** = P<0.01, Dunnetts test. From Ref 49.*

PYY, Y2 AGONISTS AND GASTROINHIBITION; THE JLEAL BRAKE"

• The exposure of the intestinal lumen to fatty acids elicits a powerful inhibition of gastric motility. This phenomenon has been termed the "ileal brake" and its mechanism has been under investigation since the 1920's. Kosaka and Lim (54, 55) established that this ileal brake mechanism was, at least in part, hormonal, and that putative hormonal mediators isolated from the intestine possessed significant gastro-in-hibitory properties. This general class of inhibitory mediators were termed "enterogastrones". Considerable evidence has been collected in support of PYY as the principal mediator of this ileal brake effect (4, 5, 17, 26, 27). It is released by ileal endocrine cells in response to luminal fatty acid stimulation (5,6). When administered into the circulation, PYY evokes a strong, vagally mediated inhibition of proximal digestive functions (5, 56).

A dense concentration of PYY binding sites is located in the DVC; the site of vago-vagal reflex control circuitry responsible for the vagal modulation of proximal digestive tract functions. Recent investigations have revealed that the DVC does not have a significant vascular diffusion barrier (24-26). Thus, peptides of the PP family have no difficulty gaining access to the extracellular spaces of the DVC.

Our studies with low doses of PYY applied directly to the DVC support the concept that the "enterogastrone" effects of PYY are mediated through the vagal innervation of the stomach. That is, (0 over a dose range consistent with physiological levels (4, 17, 27), PYY produces a profound inhibition of vagally mediated gastric motility, (zz) gastroinhibitory effects of DVC PYY are duplicated by the Y2 agonist, and *(in)* neurophysiological studies (27) suggest that the PYY and Y2 agonist-evoked vagal gastroinhibition may be produced by direct inhibition of gastric DMN neurons.

CENTRAL VAGAL GASTROEXCITATORY ACTIONS OF PYY AND NPY; ACTION AT THE Y1 RECEPTOR.

• In spite of the strong evidence that PYY or its Y2 receptor analog are associated with a vagally mediated inhibition of gastric function, other evidence provided support for PYY and NPY as potential activators of gastric motility, also through a central vagal efferent mechanism (27, 28). In these studies, higher doses of PYY delivered to the DVC evoked a significant stimulation of gastric motility. Geoghegan *et al* (29) and Lee *et al* (30) showed that ventricular injections of relatively high doses of NPY yielded significant increases in

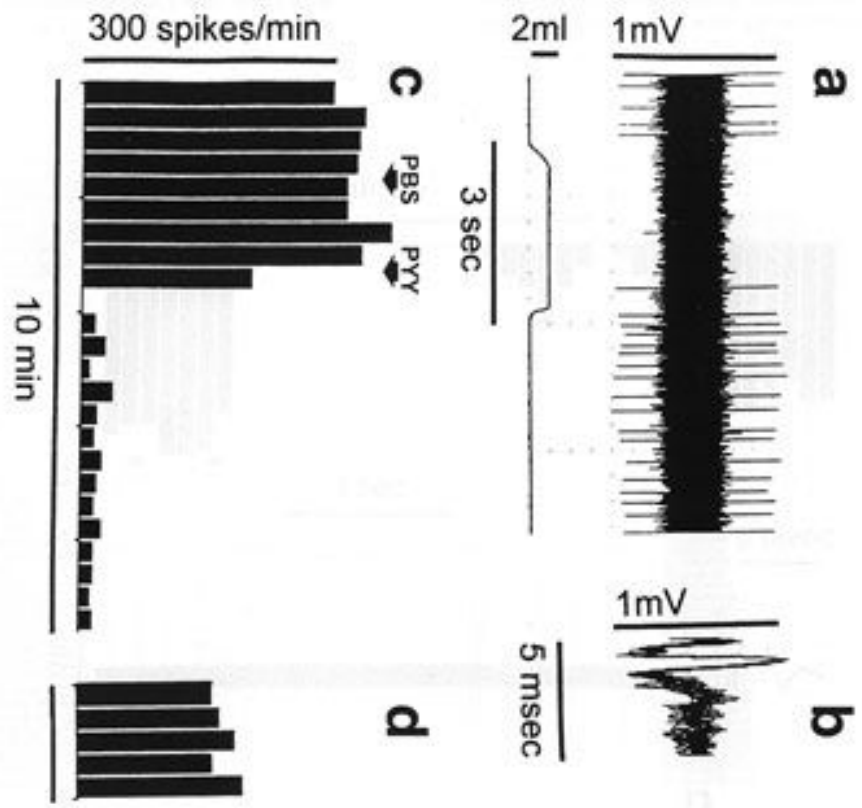

Figure 5. *PYY inhibits spontaneous firing of a physiologically-identified DMN neuron. Physiological identification of a DMN neuron* ***(a)****. Spontaneous activity of the DVC cell (upper trace) is blocked by a brief inflation of the antral balloon (lower trace); these cells are almost always, 90% of cases, DMN neurons (21, 22). Ten, superimposed, spontaneous spike traces of the neuron recorded in panel A* ***(b)****, illustrating the unitary nature of the recording. Rate histogram of DMN activity in response to application of PBS (250 pL) and PYY (0.25 fmol in 250 pL) (c). Continuation of rate histogram after a 10 minute break showing recovery of neuronal activity* ***(d)****. From Ref 53.*

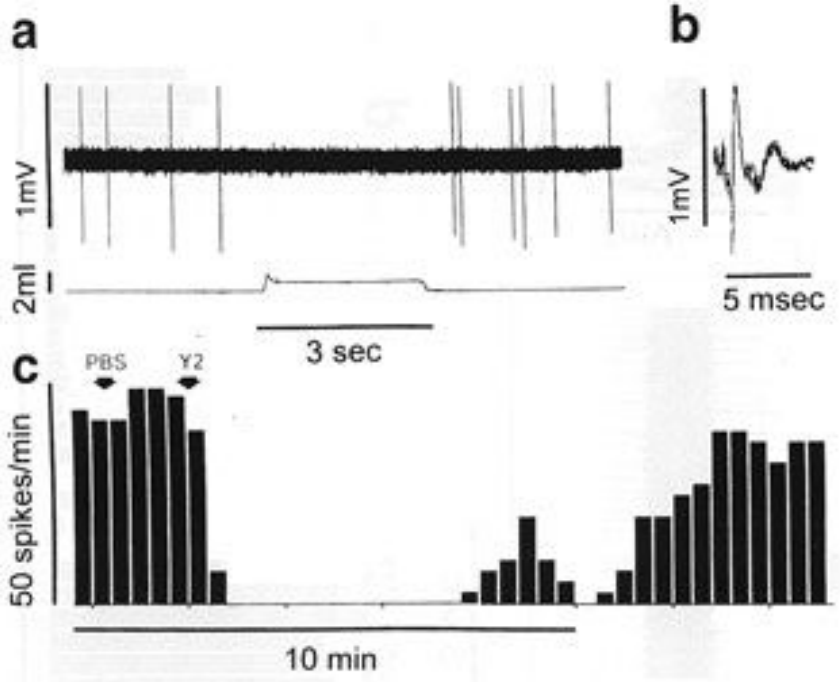

Figure 6. *Y2 agonist (PYY 13-36) inhibits spontaneous firing in a physiologically-identified DMN neuron. Physiological identification of a DMN neuron (**a**); inhibition of neuronal activity (upper trace) by antral inflation (lower trace). Ten, superimposed, spontaneous spike traces showing the unitary nature of the unit recording in panel A (**b**). Rate histogram of DMN activity in response to application of PBS (250 pL) and Y2 agonist (0.25 fmol in 250 pL) (c). From Ref 53.*

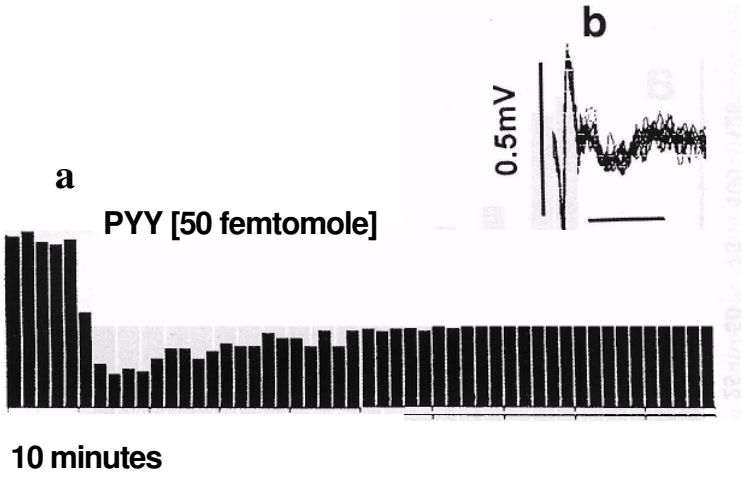

Figure *7. In vitro recording from a DMN neuron in the brainstem slice: inhibitory effect of PYY. Rate histogram showing the effects of PYY (50 fmol) on the spontaneous firing behavior of a DMN neuron recorded in the in vitro brainstem slice preparation under synoptic blockade conditions, i.e. high* Mg^{++}*/low* Ca^{++} *media (a). Ten, superimposed, spontaneous DMN action potential of same cell depicted in panel A, showing the unitary nature of the spike recording (b). From Ref 53.*

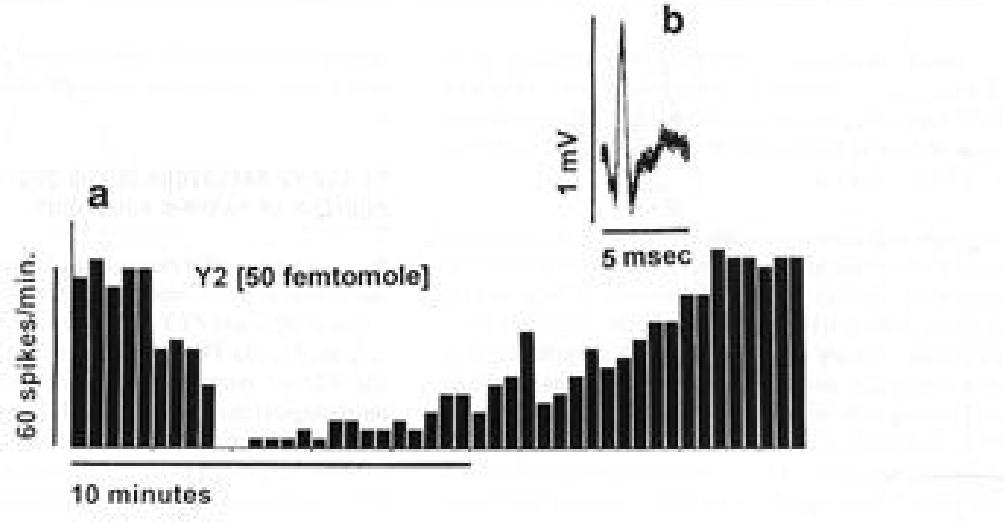

Figure 8. *In vitro recording from a DMN neuron illustrating the inhibitory effects of the Y2 agonist PYY 13-36. Rate histogram showing the effects of Y2 agonist (50 fmol) on the spontaneous firing behavior of a DMN neuron recorded in synaptic blockade media (a). Ten superimposed spontaneous DMN action potentials of same cell as in panel A, showing unitary nature of the recording (b). From Ref 53.*

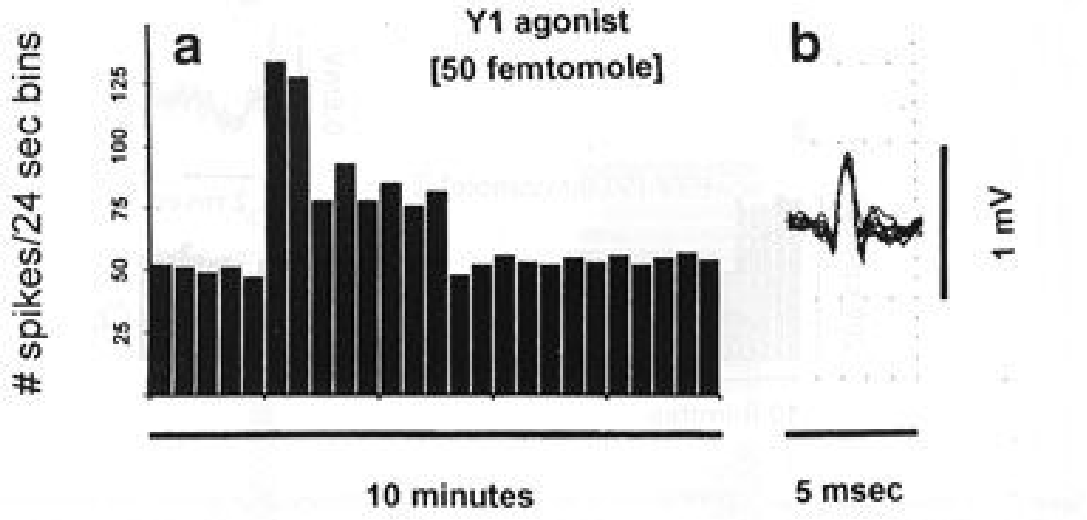

Figure 9. Effects of Yl agonist on DMN activity recorded in the in vitro brainstem slice preparation. Rate histogram showing the effects of Yl agonist (50 fmol) on the spontaneous firing behavior of a DMN neurons recorded in synaptic blockade media (a). Ten, superimposed, spontaneous DMN action potentials of same cell as recorded in panel A, showing the unitary nature of the recording (b).

gastric motility, acid secretion and pancreatic secretion, all of which were vagally mediated. These investigators proposed that NPY was acting as part of a mechanism, which connects the onset of feeding behavior with the onset of the "cephalic phase" of digestion control.

Considerable experimental evidence links NPY with the central control of feeding behaviour. NPY microinjected into the paraventricular nucleus of the hypothalamus, or other nearby diencephalic regions which participate in the control of feeding behaviour, strongly elicits eating. NPY is synthesized in hypothalamic nuclei and released under conditions known to increase feeding behaviour, i.e. growth, pregnancy, and starvation (12). Blockade of synthesis of NPY or its receptors reduces feeding behaviour (15, 57, 58). Furthermore, there are significant NPYergic inputs to the DVC region of the brain-stem (11, 43). Given that NPY is strongly associated with the initiation of feeding behaviour, it seems reasonable to also expect descending NPYergic co-control of autonomic functions which augment digestion. However, in spite of the ideological arguments and experimental data in support of this mechanism (29, 30), there are a number of reports which suggest that the central application of NPY, like PYY, could also produce a reduction in gastric motility or secretion (33-35).

Y1 AND Y2 RECEPTORS IN THE DVC: RECIPROCAL CONTROL OF GASTRIC FUNCTION?

• One possible explanation for the conflicting nature of the effects of these peptides on gastric function involves the action of NPY and PYY on Y1 *versus* Y2 receptors in the DVC (27, 48, 49, 53). Perhaps these two receptor populations (Yl and Y2) are normally segregated by morphological and/or physiological mechanisms which break down under experimental circumstances. For example, much of the PYY released from the ileum is rapidly converted to a specific Y2 agonist (PYY 3-36) by aubiquitous diaminopeptidase (DAP-IV) (57). Under physiological conditions, PYY released into the circulation would ordinarily not exist long as a combined Y1-Y2 agonist, i.e. native PYY, thus eliminating any PYY cross-talk with Y1 and Y2 receptors. DAP-IV post-processing of peptide hormones and neurotransmitters within the central nervous system is now recognized as an important step in determining

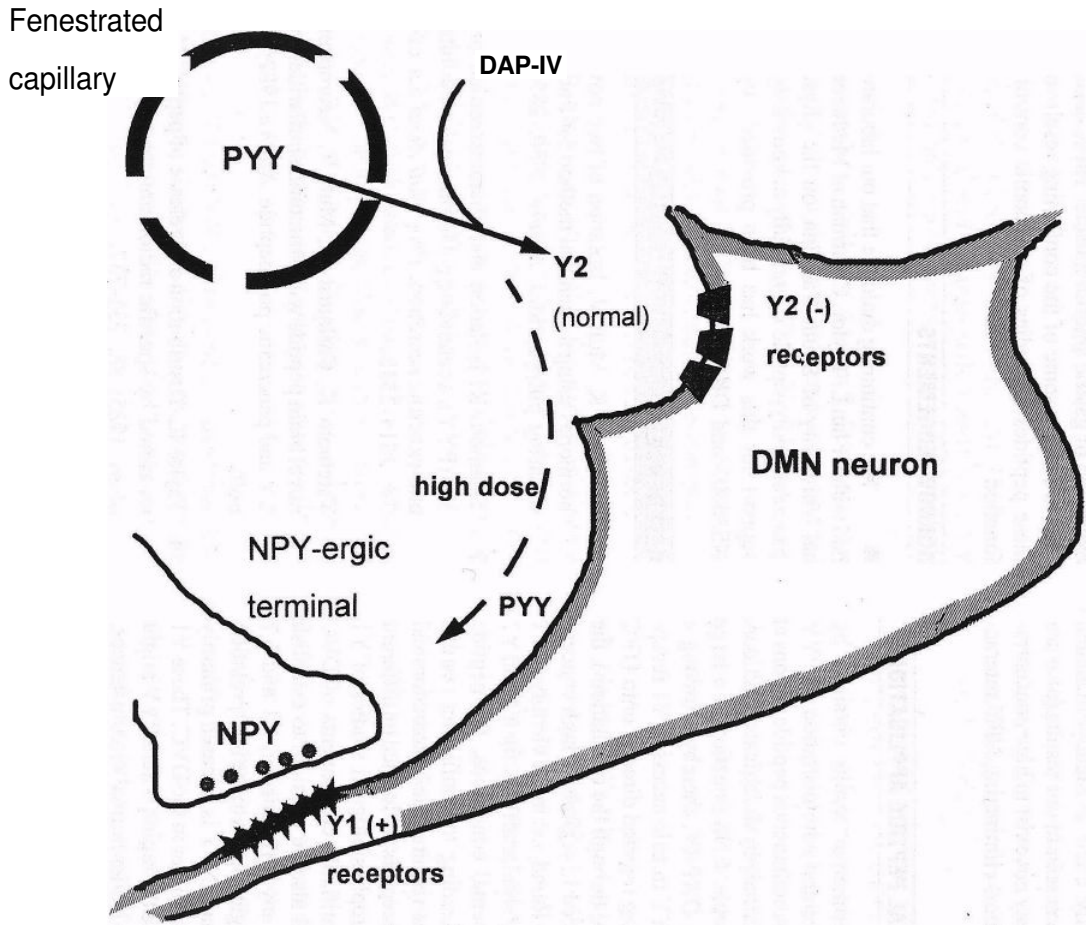

Figure 10. *Hypothetical model of the segregation of Yl and Y2 receptor effects on a DMN neut-on controlling excitatory cholinergic inputs to the digestive tract. Under normal physiological conditions, PYY released into the circulation is largely converted to a specific Y2 agonist by the action of DAP-IV. Activation of the Y2 receptor leads to inhibition of the DMN neuron, and a reduction in cholinergic excitation of the digestive tract. However, high doses of PYY injected experimentally onto the DMN neuron will also activate Yl receptors. The result can be paradoxical effects on cholinergic control of digestion, since PYY has a similar binding affinity for both Yl and Y2 receptors. NPY released onto Yl receptors activates the DMN neuron and increases cholinergic excitation of the digestive tract. This would be appropriate if NPYergic; pathways act together to augment digestion and feeding behaviour at the same time. As before, the experimental injection of NPY onto this neuron will activate both the Yl and Y2 receptors with confusion being the likely result*

specific peptide actions (59, 60). Further, Y2 receptors might exist in higher concentrations than Yl receptors in areas of the DVC that are more accessible to circulating peptides, increasing the probability that circulating PYY or its Y2 analog would elicit a Y2-mediated suppression of vagal cholinergic influences on the digestive process (23, 42). Conversely, NPY may normally be released as a neurotransmitter exclusively onto Yl receptors within the DVC. In this case, NPY would typically elicit a vagally mediated increase in digestive functions as seen in our results (also see 29, 30). In other words, NPY may not exist in high concentrations outside synapses at Yl sites, eliminating NPY interaction at Y2 receptors (Fig. 10).

CONFOUNDS OF EXPERIMENTAL PEPTIDE APPLICATION

• The conflicting experimental results obtained by different doses and routes of central administration of PYY and NPY may be explained by simultaneous peptide actions at Y1 and Y2 sites which, under normal physiological conditions, may never occur (7). For example, CNS injection of a large amount of PYY may saturate DAP-IV, thereby allowing a significant amount of native PYY to gain access to Yl recep tors. Further, since PYY is being injected directly onto DVC structures (as opposed to arrival through the circulation), the peptide may be artificially placed in regions at high concen trations where it is not normally found, i.e. in the vicinity of Yl receptors. Since PYY has a very similar affinity for Y1 and Y2 receptors (13), under experimental conditions, the peptide may activate both receptors, leading to conflicting results. Proof of this speculative scheme requires the histoanatomical demonstration that Y1 and Y2 receptors are located on different components of the DVC. Neurophysiological studies of Yl and Y2 agonist action on identifiable components of DVC motility regulation circuits will also be required to establish the functional significance of any difference in Yl and Y2 receptor distribution. Similar logic applies to the interpretation of central actions of NPY. Perhaps NPY is released primarily onto Y1 receptors as a neurotransmitter in the DVC. These Y1 receptors may be located outside the region where PYY might gain access *via* the circulation. Under normal circumstances, NPY would activate digestive functions *via* action on vagal mechanisms. Under experimental conditions, however, microinjection of NPY into the DVC would place it in contact withboth Yl and Y2 receptors. As with PYY, NPY has a nearly equivalent affinity for both YlandY2 receptors. Thus, the results of an application of NPY to the DVC by microinjection could be dependent upon the prevailing experimental conditions, e.g. basal *versus* stimulated motility. Critical histoanatomical and neurophysiological studies will be required to support or refute this hypothetical model .

CONCLUSION

• The vagal gastroinhibitory effects of PYY and NPY may be mediated by the Y2 receptor while the gastroexcita-tory effects of these same peptides may be mediated by the Yl receptor. The ultimate effects of Y2 and Yl receptor activation are inhibition and excitation, respectively, of DMN neurons which are responsible for controlling the cholinergic excitation of gastric smooth muscle. These observations may help to resolve some of the conflicting results obtained with these peptides in studies of autonomic control of digestive function.

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