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Neural modulation of the antisecretory effect of peptide YY in the rat jejunum

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Abstract

The endocrine and neural peptide, peptide YY, inhibits intestinal secretion of water and electrolytes in several animal species and in man. Peptide YY receptors have been evidenced on isolated rat jejunal crypt cells, but neural receptors are also likely to participate in the antisecretory effect of peptide YY in vivo. The aim of the present study was to investigate the mechanisms of the peptide YY effect on vasoactive intestinal peptide (VIP)-stimulated jejunal net water flux in the rat. Antagonist experiments using several drugs affecting neurally mediated processes were done for the purpose. A small peptide YY dose (10 pmol/kg) inhibited significantly ($P < 0.005$) the jejunal net water flux produced by 30 μg/kg per h of VIP. The inhibitory effect of peptide YY was suppressed, or strongly and significantly reduced, by tetrodotoxin, hexamethonium, lidocaine, idazoxan and BMY14,802 (51-(4-fluorophenyl)-4-(-4-(5-fluoro-2-pyrimidinyl)-1-piperazinyl)-1-butanol), whereas devazepide and L-NAME (L-ω-*N*-arginine methyl ester) had no effect. These results suggest that peptide YY inhibits VIP-stimulated jejunal net water flux in vivo through a neural mechanism implicating the participation of nicotinic synapses, α_2-adrenoceptors and σ receptors. © 1997 Elsevier Science B.V.

Keywords: Peptide YY; Intestinal secretion; VIP (vasoactive intestinal peptide); Intestinal nerve; α_2-Adrenoceptor; σ Receptor; (Rat)

1. Introduction

Peptide YY is a 36-amino-acid gut peptide mainly produced in L type endocrine cells of the distal small intestine, colon and rectum (Tatemoto, 1982). More recently, the presence of peptide YY has also been evidenced in gut intrinsic neurons in the dog (Mc Donald et al., 1993). Peptide YY has a number of pharmacological effects on the digestive tract, including inhibition of gastrointestinal motility and secretions (Sheikh, 1991). In the small intestine, peptide YY potently inhibits electrolyte and water secretion in different animal species and in man (Saria and Beubler, 1985; Cox et al., 1988; Playford et al., 1990).

Although the antisecretory effect of peptide YY on small intestine has been described repeatedly, little is known about its exact mechanism in vivo.

In vitro data indicate that neuropeptide Y Y_2 receptor-like, peptide YY-preferring receptors are present on basolateral membranes of rat jejunal crypt cells (Laburthe et al., 1986; Servin et al., 1989). However, it is not clear whether peptide YY effects in vivo take place only through the occupation of enterocyte receptors, or rather by activating indirect neural mechanisms modulating epithelial cell function. Such a hypothesis rests upon two lines of evidence.

First, the inhibition of jejunal secretion in vivo by a series of peptide YY derivatives with various specificities for neuropeptide Y receptor subtypes indicates that neuropeptide Y Y_1 receptor agonists, as well as neuropeptide Y Y_2 receptor agonists and to some extent pancreatic polypeptide, all inhibit rat jejunal secretion while the enterocyte receptors have very little affinity for neuropeptide Y Y_1 receptor agonists and for pancreatic polypeptide (Souli et al., 1997).

Second, the effect of peptide YY and of neuropeptide Y on intestinal secretion is seriously affected by neural antagonists under several conditions. In mouse jejunum in Ussing chambers, the peptide YY-induced decrease of basal

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short-circuit current is blocked by tetrodotoxin, chlorisondamine and haloperidol (Rivière et al., 1993). In the rat, the jejunal antisecretory effect of neuropeptide Y in vivo is decreased by tetrodotoxin and the somatostatin receptor antagonist, cyclosomatostatin (Rivière et al., 1995), while in human volunteers, haloperidol suppresses peptide YY inhibition of prostaglandin E_2-induced jejunal secretion (Rozé et al., 1997).

The purpose of the present work was to investigate whether intrinsic or extrinsic neurons participate in the antisecretory effect of peptide YY in the rat jejunum in vivo. We used as a model vasoactive intestinal peptide (VIP)-stimulated jejunal loops in situ and investigated whether a series of neural antagonists would interfere with the peptide YY effect. In order to avoid difficulties of interpretation, we first determined the effects of these various neural antagonists on basal and VIP-stimulated jejunal net water flux. We then tested against peptide YY only the antagonists which had sufficiently small effects of their own on basal or VIP-stimulated net water flux to allow a clear interpretation of their modulation of the peptide YY effect.

Part of these results have appeared in abstract form (Souli et al., 1996b).

2. Materials and methods

2.1. Animals

Male Wistar rats weighing 180–200 g, (Iffa-Credo, Les Oncins, L'Arbresle, France), were fasted for 24 h with free access to water before the experiments.

2.2. Drugs and chemicals

Peptide YY (pig, rat) and VIP (human, porcine, rat) were purchased from Neosystem (Strasbourg, France). Devazepide was generously supplied by Dr. P.S. Anderson (Merck Laboratories, West Point, PA, USA); BMY 14,802 (51-(4-fluorophenyl)-4-(-4-(5-fluoro-2-pyrimidinyl)-1-piperazinyl)-l-butanol) was a generous gift of P. Rivière (IRJ, Fresnes, France); tetrodotoxin was purchased from Alexis, France; L-NAME (L-*ω*-*N*-arginine methyl ester), prazosin, atropine sulphate, propranolol, hexamethonium and bovine serum albumin were purchased from Sigma (St. Louis, MO, USA); idazoxan was a gift from Reckitt and Colman (Kingston upon Hull, UK); lidocaine (Xylocaïne® 1%) was purchased from Astra France (Nanterre, France) and haloperidol (Haldol®, 5 mg/ml) from Janssen (Boulogne-Billancourt, France).

Peptide solutions were prepared in 0.9% NaCl containing 0.3% bovine serum albumin to limit peptide adherence to the tube lining. Prazosin was dissolved in warm absolute ethanol and diluted in 0.9% NaCl. Tetrodotoxin was dissolved in 0.1 M citrate buffer (pH 4.8), stored at −20°C and diluted with 0.9% NaCl just before the experiment. The other drugs were dissolved in 0.9% NaCl.

2.3. Experimental design

2.3.1. Jejunal ligated loop in situ

Jejunal ligated loops were prepared as described in detail in (Souli et al., 1996a). Briefly, in pentobarbital-anaesthetized rats (50 mg/kg i.p.), a closed loop of proximal jejunum (20 cm long) was tied off and filled at time zero with 2 ml of 0.9% saline. Care was taken during the preparation of the loop to protect the marginal artery of the bowel from damage and to maintain as far as possible the normal anatomical placement of the loop. The jejunal loop was returned to the abdomen which was then closed. After 30 min, the rats were killed, the jejunal loop was taken out and the amount of fluid remaining was measured by weighing the full and the empty loop, allowing calculation of the net water flux. Under these conditions the net water flux was negative, indicating a net absorption. that will be called 'basal net water flux'.

2.3.2. Treatments

To more clearly evidence the antisecretory effect of peptide YY, the basal absorption was counteracted with VIP (30 μg/kg per h = 9 nmol/kg per h) infused intravenously (saphenous vein) at 2.5 ml/h for 30 min (from $t = 0$ to $t = 30$ min). The dose was chosen so as to nearly completely suppress basal absorption under our experimental conditions (Souli et al., 1996b). The net water flux measured with VIP infusion is termed 'VIP-stimulated net water flux'.

Peptide YY was administered as an i.v. bolus injection of 10 pmol/kg, 15 min before starting the VIP infusion. This protocol was previously shown to produce about 60% reduction of the VIP effect (Souli et al., 1997). The following antagonists were intravenously injected 5 min before peptide YY: tetrodotoxin 5 μg/kg, hexamethonium 6.7 mg/kg + 6.7 mg/kg per h, atropine sulphate 0.1 mg/kg, idazoxan 0.3 mg/kg, prazosin 0.5 mg/kg, propranolol 1 mg/kg, haloperidol 1 mg/kg and BMY 14,802 10 mg/kg. Lidocaine (0.1 mg/ml) was added to the intraluminally injected 2 ml of NaCl 0.9%. Antagonist doses were chosen on the basis of previous data from our laboratory (Nagain et al., 1995) or from others (Pascaud et al., 1993). Bilateral truncal vagotomy was performed in the neck, 30 min before injection of peptide YY.

Several control groups were set up to determine the effect of antagonists per se on basal and VIP-stimulated net water flux. The complete study of an antagonist thus involved a total of six groups: in the first three groups, net water flux was measured after infusion of saline (basal net water flux), VIP (VIP-stimulated net water flux) and VIP + peptide YY (VIP + peptide YY net water flux) without antagonist; three similar groups were studied after administration of the antagonist.

2.4. Expression of results and statistical analysis

The weight difference between the full (F, mg) and the empty loop (E, mg), the measured loop length (L, cm) and the amount of saline placed in the loop at the beginning of the experiment (2000 μl) allowed calculation of the net water flux: $(F-E-2000)/L$, that was expressed as μl/cm per 30 min (assuming that 1 μl saline = 1 mg). Net absorption is indicated by a negative value and net secretion by a positive value.

In each series of six groups the effect of antagonist was determined by comparing the net water flux with and without antagonist after infusion of saline, VIP and VIP + peptide YY, by analysis of variance (ANOVA) followed by Dunnett's test. Differences with $P < 0.05$ were considered significant.

3. Results

3.1. Effect of neural antagonists on basal and VIP-stimulated jejunal net water flux

Tetrodotoxin, hexamethonium, lidocaine, idazoxan, BMY 14,802, devazepide and L-NAME did not significantly change basal absorption (Table 1, two leftmost columns). Likewise, the VIP-stimulated net water flux measured after these antagonists did not differ significantly from that without antagonist (Table 1, two rightmost columns). However, the VIP-stimulated net water flux with or without antagonist was always significantly different ($P < 0.005$) from the basal water flux measured in the respective control group (Table 1: column 3 compared to column 1 and column 4 compared to column 2).

Truncal vagotomy, atropine, propranolol, prazosin and haloperidol had significant effects on both basal and VIP-stimulated jejunal secretion (data not shown). Thus, no further effort was made to investigate the effect of these drugs on peptide YY inhibition, since the interpretation of data would have been difficult.

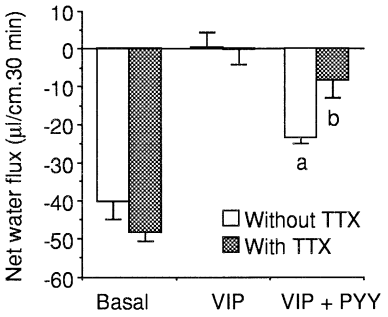

Fig. 1. Effect of tetrodotoxin (TTX, 5 μg/kg) on basal and VIP-stimulated (VIP) net water flux and on the antisecretory effect of peptide YY. Data are expressed as the net water flux in the different groups. Means ± S.E.M. in groups of 5 to 7 rats. [a] $P < 0.005$ versus VIP alone, [b] $P < 0.025$ versus VIP + PYY without TTX.

3.2. Action of neural antagonists on the antisecretory effect of peptide YY

As an example, the effect of tetrodotoxin is detailed in Fig. 1. VIP inhibited basal absorption ($P < 0.005$); PYY significantly decreased this effect ($P < 0.005$), a decrease which was counteracted by tetrodotoxin ($P < 0.025$), which had no effect in the controls or on the effect of VIP alone.

To limit the number of figures, the effect of the other antagonists on the antisecretory effect of peptide YY is summarized in Fig. 2. The antisecretory effect of peptide YY was counteracted by hexamethonium, an antagonist of nicotinic receptors ($P < 0.005$) and by lidocaine, an agent inhibiting locally neural conduction in small diameter unmyelinated fibres ($P < 0.025$).

The antisecretory effect of peptide YY was also counteracted by the α2-adrenoceptor antagonist, idazoxan ($P < 0.005$) and by the σ receptor antagonist, BMY 14,802 ($P < 0.005$).

The CCK_A receptor antagonist, devazepide, and the NO

Table 1
Effect of neural antagonists on basal and VIP-stimulated net water flux in the rat jejunum

Antagonists	Net water flux (μl/cm per 30 min)			
	Basal		Vip-stimulated	
	No	Yes	No	Yes
Tetrodotoxin	−40.6 ± 4.3 (7)	−48.7 ± 1.9 (7)	0.4 ± 3.8 [a] (7)	−0.3 ± 4.0 [b] (5)
Hexamethonium	−45.8 ± 3.4 (7)	−53.6 ± 2.2 (6)	1.6 ± 3.2 [a] (7)	−10.6 ± 5.3 [b] (6)
Lidocaine	−41.8 ± 4.6 (5)	−48.9 ± 2.3 (5)	−14.7 ± 2.4 [a] (6)	−17.2 ± 3.9 [b] (7)
Idazoxan	−44.0 ± 3.0 (6)	−51.2 ± 4.4 (7)	1.3 ± 2.7 [a] (10)	−3.7 ± 3.7 [b] (6)
BMY 14,802	−44.3 ± 3.5 (6)	−43.7 ± 4.6 (5)	1.3 ± 2.7 [a] (10)	−3.1 ± 3.6 [b] (5)
Devazepide	−46.4 ± 3.0 (8)	−50.8 ± 4.2 (5)	0.8 ± 3.1 [a] (10)	2.3 ± 3.9 [b] (5)
L-NAME	−46.4 ± 3.0 (8)	−41.4 ± 2.4 (5)	0.8 ± 3.1 [a] (10)	1.5 ± 5.5 [b] (5)

Neither basal, nor VIP-stimulated net water flux was changed by the antagonists listed herein. Values are means ± S.E.M. (number of rats in parentheses).
[a] $P < 0.005$ compared to basal net water flux without antagonist.
[b] $P < 0.005$ compared to basal net water flux with antagonist.

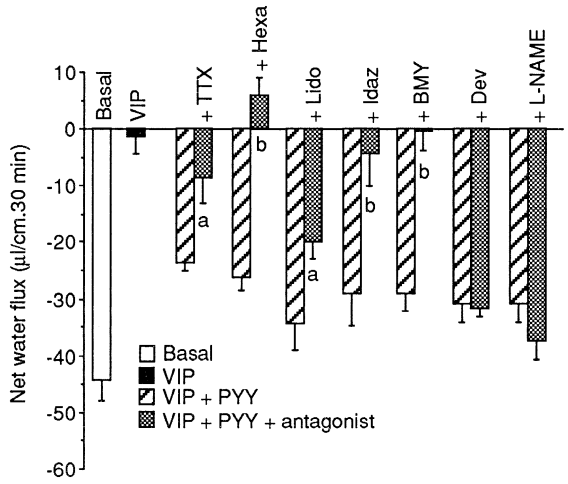

Fig. 2. Effect of neural antagonists on the antisecretory effect of peptide YY on VIP-stimulated net water flux. The effect of antagonists is shown by the difference between the net water flux after VIP + PPY + antagonist and the respective control group VIP + PYY without antagonist. The inhibitory effect of peptide YY on VIP-stimulated jejunal net water flux was significantly reduced by tetrodotoxin (TTX), hexamethonium (Hexa), lidocaine (Lido), idazoxan (Idaz) and BMY 14,802 (BMY). It was not modified by devazepide (Dev) and L-NAME. To simplify the figure, basal and VIP-stimulated net water flux are shown as the mean of the seven control groups without antagonist. As shown in Table 1, these values were not significantly altered by the antagonists mentioned here. Means ± S.E.M. in groups of 5 to 7 rats; [a] $P < 0.025$, [b] $P < 0.005$ versus VIP + PYY without antagonist.

synthase inhibitor, L-NAME, did not counteract the antisecretory effect of peptide YY.

4. Discussion

The present study was designed to investigate whether the intrinsic or extrinsic nervous system participates in the inhibitory effect of peptide YY on VIP-stimulated jejunal net water flux in anaesthetized rats. For this purpose, we combined certain neural antagonists with the intravenous injection of 10 pmol/kg of peptide YY, a dose which significantly inhibited VIP-stimulated jejunal net water flux and measured whether the antagonists would affect the peptide YY effect.

In the present experiments the neuropeptide VIP was chosen to stimulate intestinal secretion. This agent is currently believed to induce chloride secretion by intestinal crypt cells through Gs protein activation of cyclic AMP production (Laburthe and Amiranoff, 1989). VIP is a physiological stimulus in that it is present in and released by submucosal neurons innervating intestinal mucosa. In addition, the VIP dose used in the present study (30 µg/kg per h = 9 nmol/kg per h) was comparatively small and was chosen on the basis of our recent data (Souli et al., 1996a) showing that this VIP dose suppressed most of basal water absorption, or produced only slight secretion. This dose did not induce marked secretion or diarrhea and its effect can thus be considered as near to physiological conditions.

We first determined the effects of several neurally acting agents on basal and VIP-stimulated intestinal net water flux. In order to avoid complex interpretations, the results were retained only when the antagonists had sufficiently small effects of their own on basal and VIP-stimulated net water flux. The effects of the antagonists against the peptide YY antisecretory effect could then be interpreted without being obscured by effects on basal absorption or on VIP stimulation.

While peptide YY was first thought to be mainly a gastrointestinal hormone present in L-cells of the distal small intestine, colon and rectum, data now indicate that peptide YY is also present in neurons of the enteric nervous system (Mc Donald et al., 1993; Sundler and Böttcher, 1993; Böttcher et al., 1993). Peptide YY-immunoreactive neurons were found all along the dog gastrointestinal tract, from stomach to colon (Iesaki et al., 1995), while other data also indicated the presence of peptide YY neurons and peptide YY receptors in brain (Ekman et al., 1986; Leslie et al., 1988; Hernandez et al., 1994). These findings suggest that peptide YY may participate as a neurotransmitter in both enteric and central nerves, and explain why complex interactions with enteric neurons can occur.

Many studies performed in vivo (Saria and Beubler, 1985; Playford et al., 1990; Okuno et al., 1992; Bilchick et al., 1993; Souli et al., 1996a) and in vitro (Friel et al., 1986; Hubel and Renquist, 1986; Cox et al., 1988; Brown et al., 1990; Holzer-Petsche et al., 1991; Rivière et al., 1993; Eto et al., 1995) demonstrated that peptide YY and the closely related peptide, neuropeptide Y, inhibit intestinal secretion in animals and in man. Results of some of these studies suggested that peptide YY and neuropeptide Y might act on intestinal secretion indirectly via nerves (Brown et al., 1990; Rivière et al., 1993).

The mechanisms of peptide YY action seem different according to the species and to the experimental design used (basal or stimulated secretion). In vitro, the negative coupling of peptide YY-preferring receptors with the cyclic AMP production system in small intestine suggests a direct effect of peptide YY on rat enterocytes (Servin et al., 1989). Cox et al. (1988) described a tetrodotoxin- and phentolamine-insensitive peptide YY-induced decrease of the basal short-circuit current in preparations of stripped rat jejunal mucosa studied in Ussing chambers. In rabbit ileal segments arterially perfused in vitro, the proabsorptive effect of neuropeptide Y under basal conditions was blocked by yohimbine, suggesting the implication of α_2-adrenoceptors (Anthone et al., 1990). In porcine jejunal mucosa in Ussing chambers, the inhibitory effect of neuropeptide Y on basal and cAMP-stimulated short-circuit current was abolished by tetrodotoxin, and the inhibitory effect of neuropeptide Y on basal short-circuit current was reduced by phentolamine (Brown et al., 1990). More re-

cently, Rivière et al. (1993) reported that the effect of neuropeptide Y on the basal short-circuit current in mouse jejunum was insensitive to adrenoceptor antagonists, selective dopamine receptor antagonists (D_1 and D_2) and naloxone, but was decreased by haloperidol and suppressed by tetrodotoxin. In vivo in rats, neuropeptide Y inhibition of VIP-induced jejunal secretion was suppressed by σ receptor antagonists and by cyclosomatostatin (Rivière et al., 1995). Finally, peptide YY inhibition of prostaglandin E_2-induced jejunal secretion in normal volunteers was suppressed by haloperidol (Rozé et al., 1997). Thus, although the effects of peptide YY and neuropeptide Y on intestinal secretion appear neurally mediated in vivo, the mediators involved in the intestinal neurons seem different in different species.

Our present results show that the inhibitory effect of peptide YY on jejunal net water flux was totally suppressed by the nicotinic receptor antagonist, hexamethonium, and strongly decreased by the specific Na^+ channel blocker, tetrodotoxin. This suggests that peptide YY activated neural pathways comprising at least one nicotinic synapse. These results agree with those of Rivière et al. (1993, 1995) and of Brown et al. (1990).

The antisecretory effect of peptide YY was also decreased by intraluminal lidocaine, a local anaesthetic agent. However, the Na-channel blocking effect of local anaesthetic agents does not discriminate between thin, unmyelinated, intestinal sensory and motor nerve fibres (Ritchie and Greene, 1990). The counteracting effect of lidocaine on the antisecretory effect of peptide YY thus confirms the effect of tetrodotoxin and indicates in addition that local jejunal unmyelinated fibres are involved in the antisecretory effect of peptide YY.

The peptide YY effect was also suppressed by the σ receptor antagonist, BMY 14,802, and strongly decreased by the α_2-adrenoceptor antagonist, idazoxan. These results suggest that the complex neural circuitry activated by peptide YY receptors involves both σ receptor and α_2-adrenoceptors.

It is still difficult to propose a hypothetical scheme for the neural connection which might occur because localization of the receptors involved is not known. While α_2-adrenoceptors and peptide YY receptors have been evidenced both on intestinal crypt cells (Paris et al., 1990) and on nerves σ receptors have not been shown on epithelial cells and most of the available evidence suggests their presence on neurons (Coccini et al., 1991). Although their receptors seem different (Tam and Mitchell, 1991), peptide YY and σ receptor agonists probably activate neural processes sharing common intermediates, since many effects of σ receptor agonists are reproduced by neuropeptide Y or peptide YY and since the σ receptor antagonist BMY 14,802 blocks many of neuropeptide Y and peptide YY effects (Junien et al., 1991; Gué et al., 1992a,b; Pascaud et al., 1993). The successive activation by peptide YY of receptors of a first neuron, possibly sensitive, although this remains hypothetical and then, through a nicotinic synapse, of extrinsic noradrenergic neurons finally acting on crypt cells may be suggested.

In conclusion, this study demonstrated that peptide YY inhibits VIP-stimulated jejunal net water flux in rats via a neural mechanism implicating nicotinic synapses, α_2-adrenoceptors and σ receptors.

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