available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/peptides

Review

Peptide YY: A neuroendocrine neighbor of note

Helen M. Cox *

Wolfson Centre for Age-Related Diseases, King's College London, School of Biomedical and Health Sciences, Guy's Campus, Hodgkin Building, London SE1 1UL, UK

ARTICLE INFO

Article history:
Received 3 May 2006
Accepted 7 July 2006
Published on line 27 December 2006

Keywords:
Peptide YY
PYY(3–36)
Endocrine L-cells
Paracrine actions
Electrolyte secretion

ABSTRACT

Endocrine cells, enteric neurons and enterocytes provide an integrated functional defense against luminal factors, including nutrients, microbes and toxins. Prominent among intrinsic mediators is peptide YY (PYY) which is present in ~50% of colorectal endocrine cells and neuropeptide Y (NPY), a neurotransmitter expressed in submucous and myenteric nerves. Both peptides and their long fragments (PYY(3–36) and NPY(3–36)) are potent, long-lasting anti-secretory agents *in vitro* and *in vivo* and, they provide significant Y receptor-mediated absorptive tone in human and mouse colon mucosa. The main function of the colon is to absorb 90% of ~2 l of daily ileal effluent (in adult humans) and Y-absorptive tone can contribute significantly to this electrolyte absorption. Blockade or loss of this mucosal Y-absorptive tone (i.e. with Y_1 or Y_2 antagonists) leads to hypersecretion and potentially to diarrhea, so Y agonists are predicted to rescue absorption by mimicking endogenous neuroendocrine PYY or neuronal NPY.

Contents

1. Introduction

Peptide YY (PYY) and its degradation product, PYY(3–36) are both paracrine and hormonal members of the pancreatic polypeptide (PP) family whose levels increase significantly in tissue and plasma after a meal. This article is a summary of an invited lecture given at the eighth International Neuropeptide Y (NPY) meeting (St. Petersburg, FL, April 2006) and presents a "gut-centric" overview of PYY's paracrine effects, specifically, (i) its cellular distribution, (ii) mechanisms of release

* Tel.: +44 207 848 6182; fax: +44 207 848 6182.
E-mail address: helen.m.cox@kcl.ac.uk.
0196-9781/$ – see front matter
doi:10.1016/j.peptides.2006.07.023

and, (iii) functional consequences highlighting the specific Y receptors activated in normal human and mouse intestine (comparing these response profiles with the phenotypes exhibited by tissues from specific knockout (KO) models). Finally (iv), a summary of intestinal symptoms observed following either surgical manipulation or specific gastrointestinal (GI) diseases will provide a basis for final conclusions regarding the potential for Y-based agonists as mimics of endogenous PYY, etc., and to act therefore as novel anti-diarrheal drugs of the future.

How physiologically important are PYY and PYY(3–36) as defenders against diarrhea-causing stimuli? *In vivo* studies have shown that PYY or NPY infusion to healthy human subjects attenuate hypersecretion prestimulated by either prostaglandin E2 or vasoactive intestinal polypeptide (VIP) [30,53]. Recent studies utilizing isolated colon mucosa have shown that PYY, PYY(3–36), NPY and PP are anti-secretory and these peptides stimulate the same repertoire of Y receptors (Y_1, Y_2 and Y_4) in human and mouse tissue [11,13,32]. However, the identity of the Y receptor type(s) that are responsible for the *in vivo* effects remain unknown, through lack of clinical experimentation with selective Y receptor agonists. Since diarrhea is a symptom of increased intestinal electrolyte and fluid secretion as well as increased motility, we have been interested in ascribing specific functions to exogenous and endogenous Y peptides and their cognate receptors given the background of different peptide distributions in the GI tract.

2. Cellular distribution of PYY compared with related peptides

PYY is expressed in ~50% of colorectal endocrine L-cells in mouse [3] and human large bowel [21] and is co-localized with pro-glucagon products, glicentin and glucagon-like peptide 1 (GLP-1) and GLP-2 [19]. Sundler et al. have shown that these unrelated peptides are co-packaged in the same secretory granules [7,19] and they are co-released, at least initially when food arrives in the duodenum [2]. PYY-positive endocrine cells in human colon are often surrounded by Y_1-immunoreactive epithelia and nerve fibers, but are themselves Y_1-negative [39] thus an autocrine action for PYY is unlikely in this tissue. PYY is additionally expressed in a very sparse population of gastric neurons discrete from those expressing NPY and only found in certain species [6] notably not in human or mouse stomach. PYY-positive neurons are also found in specific regions of the central nervous system, e.g. hypothalamus, pons, medulla and spinal cord [19] and these are discrete from those expressing NPY. The peptide is also found in pancreatic endocrine cells, more often co-localized with PP and less frequently with glucagon (depending again on the species studied).

PP-positive F-cells constitute the fourth group (~10%) of pancreatic islet endocrine cells, after insulin (in beta cells) glucagon (alpha) and somatostatin (delta) cells. PP is also present in a sparse, minor population of intestinal endocrine cells, throughout the GI tract of most species studied to date [19,21]. In contrast, NPY is present in >50% of enteric submucous neurons the majority of which innervate targets in the lamina propria including the epithelial lining of all mammalian models studied to date, including rat, mouse and human colon [18,20,49,57]. NPY is a non-adrenergic, non-cholinergic neurotransmitter in the mammalian enteric nervous system and is more commonly co-localized with vasoactive intestinal polypeptide (VIP) than with any other neuropeptide, although there are variations between species and between areas of intestine in the same species [18,20,24].

3. Mechanisms of PYY release from intestinal endocrine cells

Nutrients stimulate PYY plasma levels within 30 min of ingestion of a high calorific meal (and reaching a maximum within 60 min), long before the luminal contents have reached the terminal intestine where there is a high density of PYY-positive endocrine cells [1]. Dietary fat, fatty acids, bile salts, carbohydrates and proteins all stimulate PYY release but to different degrees and with different time-courses and there is a suggestion that ileal PYY-positive endocrine cells are responsive to fewer luminal cues (oleic acid and bile salts in particular) than those in the large bowel (for full review see [48]). PYY release is also regulated by and in turn regulates, parasympathetic nerves, specifically vagal nerve activity [63] thereby indirectly modulating intestinal activity and is also sensitive to neurohormonal influences (for review see [48]).

Of the total PYY released, ~40% is thought to be converted to PYY(3–36) [26,43] which can activate Y_2 and/or Y_5 receptors in peripheral and central targets. This hydrolysis occurs relatively rapidly via dipeptidyl peptidase IV (DPP-IV; EC3.4.14.5) [16]. Thus, the biological activity of PYY is not abolished by the actions of this enzyme, rather a subtle change in pharmacology occurs from potentially three (Y_1, Y_2 and Y_5) receptors being activated by full length PYY, to co-activation of two, Y_2 and Y_5 receptors by PYY(3–36). This change in target activity may be important in modulating digestive and feeding behavior, as well as initiating satiety after eating a meal consequent to post-prandial increases in plasma PYY and PYY(3–36). DPP-IV inhibitors are of particular current interest as they are undergoing trials as new treatments for type 2 diabetes. In addition to the focus of their proposed clinical benefit, i.e. to prolong the half life on incretin hormones such as GLP-1 and GLP-2 that will lower blood glucose in a glucose-dependent manner, some of the DPP-IV inhibitor effects (i.e. promoting satiety, reducing food intake and subsequently body weight) are likely to be mediated by unrelated peptides/hormones that are also substrates for the enzyme, such as PYY. If future studies with DPP-IV inhibitors show PYY stability and plasma levels are enhanced, then potential GI side effects may include constipation and this disturbance could additionally be amplified by increased stability of other pro-absorptive DPP-IV substrates such as enkephalins.

While fat and protein ingestion produce sustained release of PYY, carbohydrates elicit a transient release profile in human subjects (maximal within 30 min) [1]. In perfused rat colon luminal amino acids, bile salts, glucose and oleate varyingly stimulate PYY release and largely by as yet uncharacterized mechanisms. Short chain fatty acids (SCFAs) that are produced through fermentation of dietary fiber by colonic microflora also cause PYY release with consequent