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Serotonin release and uptake in the gastrointestinal tract

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ABSTRACT

The afferent innervation of the gastrointestinal (GI) tract consists of intrinsic and extrinsic sensory neurons that respond to nutrients, chemicals or mechanical stimuli within the gut lumen. Most stimuli do not interact directly with the afferent nerves but instead activate specialised cells in the epithelium in a process of sensory transduction. It is thought that one of the first steps in this process is the release of serotonin (5-HT) from the enterochromaffin (EC) cells. The EC cells are a sub-type of enteroendocrine (EE) cells which are found among the enterocytes of the intestinal epithelium. The EC cells are responsible for the production and storage of the largest pool of 5 HT in the body. Released 5-HT can act on the intrinsic nerves and vagal endings. This review will focus on the role of 5-HT in sensory transduction and examine how the EC cell produces and releases 5-HT. We will explore recent developments that have helped to elucidate some of the proteins that allow EC cells to sense the luminal environment. Finally, we will highlight some of the findings from new studies using electrochemical techniques which allow the real-time recording of 5-HT concentrations near to the EC cell.

1. Introduction

The afferent innervation of the gastrointestinal (GI) tract consists of intrinsic and extrinsic sensory neurons that respond to nutrients, chemicals or mechanical stimuli within the gut lumen. Most stimuli do not interact directly with the afferent nerves but instead activate specialised cells in the epithelium in a process of sensory transduction. It is thought that one of the first steps in this process is the release of serotonin (5-HT) from the enterochromaffin (EC) cells (for reviews on the sensory transduction process, see Raybould, 2002; Bertrand, 2003; Blackshaw et al., 2007; Gershon and Tack, 2007; Grundy, 2008). The EC cells are a sub-type of enteroendocrine (EE) cells which are found among the enterocytes of the intestinal epithelium. The EC cells are responsible for the production and storage of the largest pool of 5-HT in the body (Erspamer, 1954; Gershon and Tack, 2007). Released 5-HT can act on the intrinsic nerves and vagal endings. This review will focus on the role of 5-HT in sensory transduction and examine how the EC cell produces and releases 5-HT. We will explore recent developments that have helped to elucidate some of the proteins that allow EC cells to sense the luminal environment. Finally, we will highlight some of the findings from new studies using electrochemical techniques which allow the real-time recording of 5-HT concentrations near to the EC cell.

2. 5-HT is an important paracrine signalling substance in the GI tract

Serotonergic transmission from the raphé nuclei acts on most brain areas while enteric neurons utilise 5-HT for some reflexes and synaptic potentials (e.g., Monro et al., 2002; Monro et al., 2005). It is, however, the non-neuronal EC cells that produce, store and release the largest pool of 5-HT in the body (Erspamer, 1954; Gershon and Tack, 2007). 5-HT released from the EC cells modulates a large number of GI reflexes in health and disease (for reviews see Furness et al., 1999; Kirkup et al., 2001; Bertrand, 2003; Grundy and Schemann, 2005). 5-HT and other EE cell mediators, such as cholecystokinin (CCK) or adenosine-5′-triphosphate (ATP), are thought to act in concert to initiate or maintain motor and secretory patterns tuned to the contents and to the region of intestine. For example, mechanical stimuli applied to the mucosal epithelium releases 5-HT into the lumen which enhances peristaltic reflexes (e.g., Bülbring and Crema, 1959; Kirchgessner et al., 1992; Foxx-Orenstein et al., 1996; Grider et al., 1996; Linden et al., 2003; O'Hara et al., 2004). Similarly, nutrients—such as short or long chain fatty acids, peptides, glucose—or chemical stimuli (e.g., acid, base) seem to act at the epithelial border by causing release of 5-HT from the EC cells or other sensory mediators from the EE cells (Raybould, 2002; Bertrand, 2003; Blackshaw et al., 2007; Gershon and Tack, 2007; Grundy, 2008) (Fig. 1).

Abbreviations: GI, gastrointestinal; ENS, enteric nervous system; CCK, cholecystokinin; ATP, adenosine-5′-triphosphate; EC, enterochromaffin cell; EE, enteroendocrine cell; UC, ulcerative colitis; IBS, irritable bowel syndrome; IBD, inflammatory bowel disease; 5-hydroxytryptamine or 5-HT, serotonin; SERT, serotonin reuptake transporter; TpH, tryptophan hydroxylase; 5-HTP, 5-hydroxytryptophan; 5-HIAA, 5-hydroxyindoleacetic acid; CGA, chromogranin A; GABA, gamma-aminobutyric acid; SST, somatostatin.

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The release of 5-HT from the EC cells is not always beneficial. A very high level of release is one of the main causes of symptoms such as the diarrhoea associated with cholera (Lundgren, 1998; Turvill et al., 2000), the nausea due to chemo-or radiation therapy (Sanger, 1990) or the flushing and heart palpitations associated with carcinoid tumours (McCormick, 2002). The central position of EC cells in these symptoms has led to the proposal that they contribute to similar problems associated with chronic intestinal diseases such as inflammatory bowel disease (IBD) or irritable bowel syndrome (IBS). This has led to a great deal of interest in the effects of inflammation on EC cells and the 5-HT they release (e.g., Lomax et al., 2006; Mawe et al., 2006; Keating et al., 2008). Interestingly, it is not always clear from individual measures of 5-HT levels or EC cell numbers if the overall availability of 5-HT goes up or down in such cases. For example, in early studies of ulcerative colitis (UC) patients, the numbers of EC cells decreased (e.g., Verity et al., 1962), while in later studies the numbers of EC cells increased (e.g., El-Salhy et al., 1997). More recently, Coates et al. (2004) have found that the number of EC cells decreased in patients with severe UC but found no change in mild UC or in tissues from irritable bowel syndrome (IBS) patients. In contrast, Dunlop et al. found an increase in mucosal 5-HT turnover in post-infectious IBS (Dunlop et al., 2005).

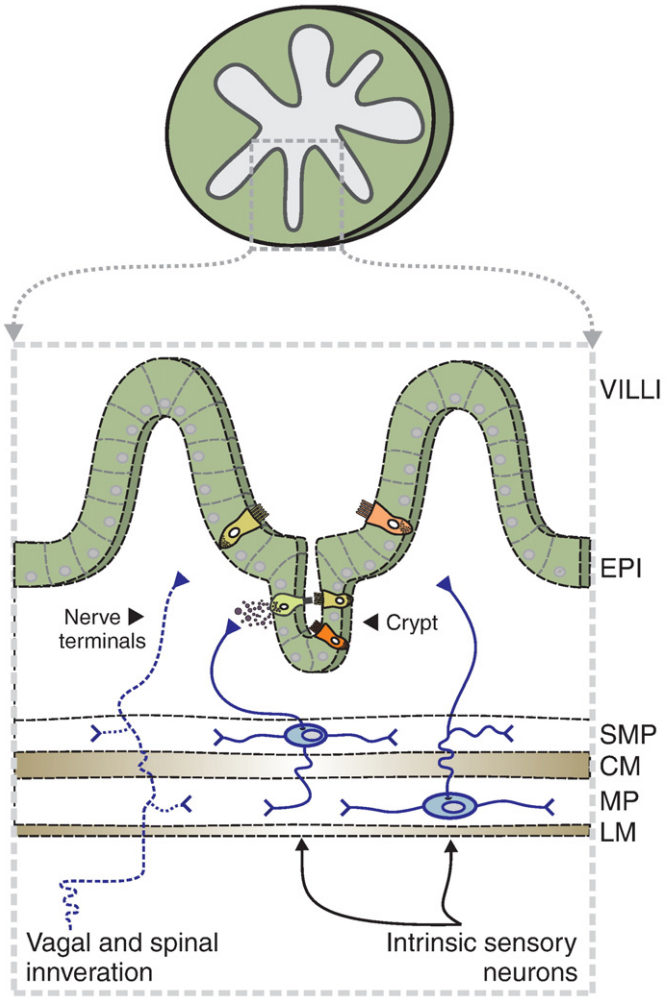

Fig. 1. Side view of the intestinal wall showing the different layers. Top, a diagram showing a section of intestine with two villi highlighted and shown in detail below. These layers are, from the top: the mucosal epithelium (EPI) which contains the enterocytes and the enteroendocrine (EE) cells—specialised epithelial cells that contain neuroactive substances located in secretory granules. Several types of EE cell are depicted (different colours) including the 5-HT containing enterochromaffin (EC) cell (depicted releasing 5-HT near to afferent nerve terminals into the underlying lamina propria). The submucosal plexus (SMP) is next, with the cell bodies of secretomotor, vasodilator, and a population of intrinsic sensory neurons. The circular muscle (CM), followed by the myenteric plexus (MP) which contains the cell bodies of motor neurons, interneurons and a population of intrinsic sensory neurons; and finally, the longitudinal muscle (LM).

Animal models of inflamed bowel have also yielded conflicting results. In a trinitrobenzene sulfonic acid (TNBS) model of mouse colitis, Linden et al. (2005a) showed increased 5-HT availability due to a decrease in serotonin reuptake transporter (SERT)-dependent 5-HT uptake with no change in EC cell numbers, while previous studies of TNBS models of guinea pig colitis and ileitis found an increase in EC cell numbers (Linden et al., 2003; O'Hara et al., 2004). On the other hand, a consistent finding of these studies was that levels of SERT expression were decreased. The central role of SERT in controlling 5-HT availability is highlighted in a new study by Bischoff et al. showing that rats lacking SERT have a much more severe TNBS induced colitis (Bischoff et al., 2009).

Several recent studies have explored the immunological link between inflammation and 5-HT availability. Wang et al. have shown that during parasitic infection a Th2-based mechanism causes an increase in the number of EC cells and the amount of 5-HT (Wang et al., 2007). In support of this, Motomura et al. have shown that a Th2-mediated inflammation causes similar changes as compared to a Th1 mediated inflammatory response to the same parasitic infection (Motomura et al., 2008). Taken together these studies show that disease state such as inflammation can strongly regulate 5-HT availability.

3. The production, release, uptake and degradation of 5-HT in the intestine

The EC cells produce 5-HT from the dietary amino acid L-tryptophan using the rate limiting enzyme tryptophan hydroxylase (TpH) (Verbeuren, 1989). In the gastrointestinal tract TpH isoform 1 has been localized to EC cells (Yu et al., 1999) while the second isoform, TpH2, has been localized to enteric neurons and central raphé neurons (Walther et al., 2003). TpH1 converts L-tryptophan to 5-hydroxytryptophan (5-HTP). The non-rate limiting enzyme L-amino acid decarboxylase (L-AADC), contained in EC cells, then converts 5-HTP to 5-HT (Hakanson et al., 1970; Verbeuren, 1989). Newly produced 5-HT is packaged into granules/vesicles by the vesicular monoamine transporter 1 (VMAT1); this isoform is specific for EC cells and a small proportion of adrenal chromaffin cells (Rindi et al., 2004; Schafermeyer et al., 2004). 5-HT is released mainly from the granules stored near the basal border of the EC cell, but some studies have also identified granules near the apical membrane (Nilsson et al., 1987) and demonstrated that 5-HT can be selectively released into the lumen (Ahlman et al., 1981; Forsberg and Miller, 1982; Fujimiya et al., 1998b) and found in the faeces (Fukumoto et al., 2003; Tsukamoto et al., 2007). What causes the release of 5-HT will be covered in detail in later sections of this review (Fig. 2).

5-HT released from the granules stored near the basal border of the EC cell enters the lamina propria where it can interact with nerve terminals, immune cells and can be taken up into the blood by the platelets. The EC cells are in constant migration from the crypt to the tip of the villus (e.g., O'Hara and Sharkey, 2007); one consequence of this is that no close contacts with nerve terminals or immune cells can be maintained. Indeed close contacts between EC cells and other structures are not common in the first place (Wade and Westfall, 1985). Thus to affect the nerve terminals, 5-HT must be released in a paracrine manner. The high concentrations of 5-HT released from the EC cell can activate the intrinsic or extrinsic sensory nerve terminals via 5-HT_3 receptors (Hillsley et al., 1998; Bertrand et al., 2000), while at lower concentrations it activates 5-HT_4 or 5-HT_{1P} receptors (Grider et al., 1996; Pan and Gershon, 2000). Many *in vitro* studies