

# The intestinal mucosa as a target and trigger for enteric reflexes

D Grundy

The gastrointestinal tract must balance the ostensibly conflicting needs of nutrient assimilation and protection against potentially harmful pathogens, enterotoxins, and antigens. Furthermore, it must provide a functional barrier for the latter but allow nutrients, electrolytes, and water to cross the mucosa readily in order to meet the eventual metabolic demands of the individual (fig 1). Apparent in these conflicting needs is the ability to sense luminal contents in order to establish, through reflex and endocrine mechanisms, the appropriate motor and secretory activity either to facilitate uptake or to dilute and rapidly expel contents through diarrhoea and/or emesis.

Enteroendocrine cells may be secondary sense cells for sensory signal transduction. Their apical microvilli could detect the mechanical and chemical environment in the lumen, and in response to an appropriate stimulus would release mediators across the basolateral membrane. These mediators could then act as paracrine agents on neighbouring cells, including the terminals of afferent fibres situated below the mucosal epithelium or act in an endocrine fashion following diffusion into the systemic circulation. The former has been proposed for both cholecystokinin (CCK), which plays a pivotal role in the reflex responses to luminal protein and lipid,<sup>1</sup> and for 5-hydroxytryptamine (5-HT) which will be discussed below. Another mechanism of afferent activation from the lumen that is pertinent for responses to luminal antigen involves mast cells but this is beyond the scope of this article.

A role for 5-HT in the intestinal secretory response to enterotoxin, and in particular cholera toxin, is well established.<sup>2</sup> Thus enterochromaffin cell degranulation and 5-HT release occur following exposure to cholera toxin while desensitisation to 5-HT or treatment with

5-HT antagonists attenuates the secretory response.<sup>3</sup>

Evidence for neural involvement in mucosal secretion stems from a wide range of investigations in which the secretory response to toxins and other stimuli, such as mucosal stroking, are blocked by ganglion blocking agents or tetrodotoxin. Antagonists of the transmitters released from secretomotor neurones of submucosal origin, of which acetylcholine and vasoactive intestinal peptide are the major transmitters, also attenuates the secretory response.<sup>4</sup>

Both intrinsic and extrinsic afferent neurones are sensitive to 5-HT. Myenteric neurones with after hyperpolarisation electrophysiology project to the mucosa and can be stimulated to generate non-synaptic action potentials by mechanical, electrical, and chemical stimulation, including 5-HT. The density of this intrinsic afferent innervation of the mucosa is high. Song *et al* (1991)<sup>5</sup> estimated that each villus was innervated by >60 Dogiel type II myenteric neurones using fibre tracing methods. Bertrand *et al* (1998)<sup>6</sup> also found massive overlap of receptive fields mapped by electrical stimulation and calculated that >230 neurones innervated the same region of mucosa.

Intrinsic sensory neurones in the submucosal plexus which synaptically stimulate myenteric neurones have been visualised using *c-fos* expression as a marker of neuronal excitation.<sup>7</sup> Using immunocytochemistry it was possible to stimulate certain cells in the submucosal and myenteric ganglia to "light up" following both physiological stimulation by mechanical distortion and the luminal application of cholera toxin. Induction of *fos* immunoreactivity in neurones by both stimuli was prevented by a 5-HT<sub>1p</sub> receptor antagonist, N-acetyl-5-hydroxytryptophyl-5-hydroxytryptophan, suggesting that endogenous 5-HT plays a role in the transduction of these luminal stimuli to intrinsic sensory activation.

Such dependence on 5-HT for reflex stimulation of intestinal secretion by cholera toxin was confirmed recently by Turvill *et al* (1998).<sup>8</sup> However, secretion stimulated by the heat labile toxin of *E coli*, while chemically closely related to cholera toxin, was not dependent on 5-HT. Thus not all enterotoxins stimulate secretion following activation of enterochromaffin cells. As both toxins acted via a hexamethonium sensitive pathway there must be different mechanisms by which enteric secretory reflexes can be triggered. Heat stable toxin from *E coli*

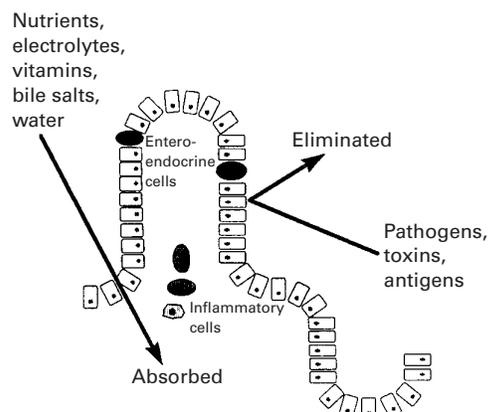


Figure 1 Conflicting mucosal functions.

Department of  
Biomedical Science,  
University of Sheffield,  
Western Bank,  
Sheffield S10 2TN, UK  
D Grundy

Correspondence to:  
Dr D Grundy,  
d.grundy@sheffield.ac.uk

**Abbreviations used in this paper:** CCK,  
cholecystokinin; 5-HT, 5-hydroxytryptamine.

Table 1 Comparison of intrinsic and extrinsic afferent innervation of the mucosa

	Intrinsic afferent	Extrinsic afferent
Cell bodies	Submucosal or myenteric plexus	Nodose or DRG
Receptive fields	8–10 mm <sup>2</sup>	Similar
Density	Overlapping	Sparse
Sensitivity to 5-HT	Yes	Yes
Modality	Mechano- and chemo-sensitivity	Mechano- and chemo-sensitivity

5-HT, 5-hydroxytryptamine; DRG, dorsal root ganglion.

(Sta) may also stimulate secretion via a mechanism independent of 5-HT but involving extrinsic afferents since the response was attenuated by treatment with the sensory neurotoxin capsaicin.<sup>9</sup>

Extrinsic afferents are also sensitive to 5-HT.<sup>10,11</sup> These afferents project from the mucosa, via the vagus nerves, to the brain stem. The sensitivity of these afferents to the 5-HT<sub>3</sub> receptor agonist 2-M-5-HT and abolition of the response by granisetron suggest that the 5-HT<sub>3</sub> receptor is the predominant (or possibly the only) receptor involved in activation of these extrinsic afferents. In contrast with innervation by intrinsic afferents, that by extrinsic afferents is limited (table 1).<sup>12</sup> Small regions of mucosa receive the arborising terminals of single vagal afferents while large areas of mucosa are without vagal afferent innervation. This suggests that the processing of intrinsic and extrinsic afferent information is different. Individual intrinsic afferents may not function alone but instead form a sensory network which influences the gain in enteric reflex pathways. In contrast, the sparse extrinsic afferent innervation may serve as a trigger function, activated under specific circumstances to bring about a stereotypic response

such as the giant retrograde contractions that occur during emesis. In this respect, one could liken the extrinsic pathway to an alarm system with little capacity for discrimination but which, once activated, triggers an extensive response.

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