

Chapter 4—Summary

Chapter 4 explores research into the structure and functional role of various cell types in the tissue surrounding enteric nerves. The cellular targets of enteric neurones include gastrointestinal smooth muscle, interstitial cells of Cajal (ICCs), neuroendocrine cells, mucosal secretory and absorptive cells, secretory glands, blood vessels, and immune cells. The variety of receptor types found on these various cells provides considerable scope for pharmacological intervention. In defining or identifying receptor types, however, attention has been drawn to the differences between the action of endogenous transmitters and those that are applied exogenously. It is important to be aware that pharmacological blockade of some pathways can lead to compensatory activity from parallel pathways, which also complicates the definition of receptor types. Regional differences may be found in different tissue layers and different parts of the same tissue layer. There are also differences between different parts of the gastrointestinal tract and between species. With these provisions in mind, data have been presented for specific tissue/organ systems.

Studies of opossum oesophageal smooth muscle indicate that the main excitatory motor pathway to the smooth muscle cells involves acetylcholine and tachykinin, while the main inhibitory pathways involve adenosine triphosphate, nitric oxide (NO), and vasoactive intestinal peptide (VIP). NO is probably the main inhibitory neurotransmitter and it may act in series with VIP. The oesophagus is unique in that its peristaltic movement is generally unidirectional. During peristalsis, the inhibitory and excitatory nerves work together to produce a very precisely timed sequence of inhibition followed by excitation.

The ICCs, as described earlier, are thought to have a functional role in pacemaking or neurotransmission. Immunohistochemical studies indicate that several classes of these cells seem to express the receptor tyrosine kinase, c-Kit. This is critical to both the development and maintenance of ICCs. The existence (in the murine gastric fundus) of specialised synapse-like contacts between enteric neurones and ICCs and the close proximity of nitric oxide synthase (NOS), vesicular acetylcholine transporter, and substance P-like neurones suggests that the ICCs are heavily innervated by excitatory and inhibitory enteric motor neurones. Thus they may provide an important pathway for communication between nerves and gastrointestinal smooth muscle, possibly by an electrocoupling process.

The gastrointestinal tract can respond rapidly to noxious luminal contents and it is thought that enteroendocrine cells may be secondary sensor cells which can sense the chemical and mechanical environment in the lumen. These cells have the ability to release mediators (mainly 5 hydroxytryptamine (5-HT)) across the basolateral membrane which act locally on neighbouring cells and nerve terminals or diffuse into the circulation and act systemically. Both extrinsic and intrinsic afferent neurones are sensitive to 5-HT and the 5-HT₃ receptor seems to be predominant. Extrinsic afferent innervation is sparser than intrinsic innervation, suggesting that the processing of

information may be different for the two types. It is probable that the sensory network of intrinsic afferents governs day to day control of luminal events and that the extrinsic afferents come into play only under specific circumstances, such as the presence of a noxious chemical or object in the gastric lumen, which requires expulsion by emesis or diarrhoea—that is, they form the emergency alarm system. When the gastrointestinal tract is subjected to chemical or physical insult, it also has to protect its own integrity, in addition to dealing with the insult. Spinal afferents constitute an emergency system that signals for an increase in microcirculatory blood flow. The local sensory neural effects are mediated by calcitonin gene related peptide and tachykinins, via the common messenger NO. The neural emergency system limits the damage to the surface of the mucosa and creates favourable conditions for healing and restitution. An understanding of how chemical injury to the stomach is signalled to the central nervous system (CNS) may have some bearing on the understanding and treatment of functional dyspepsia and other conditions where there is a sensation of discomfort. Experimental data have shown that gastric acid challenge is signalled to the brain stem, but not the spinal cord, via vagal afferents which are sensitive to acid. Hence vagal and spinal afferents seem to subservise two different respective roles, one sensing and one responding to chemical insult. Current work is underway to characterise transmitters and receptors in the afferent process of chemical insult.

The last type of specialised cell discussed in this session was the gastrointestinal mast cell which releases mediators in response to stress and allergic challenge. There is strong evidence from neuroanatomical studies that there is direct innervation of gastrointestinal mast cells. The responses to neural stimulation are heterogeneous—sympathetic stimulation inhibits mast cells while vagal stimulation activates them. Mast cell activity has also been shown to be subject to CNS modulation and this neural-mast cell “cross talk” is probably important in the regulation of epithelial responses. Studies of neuroimmune reactions suggest a major role of stress as a modulator of gastrointestinal physiology, and stress factors which involve corticotrophin releasing hormone may be relevant to the management of certain intestinal and colonic disorders. Although this hormone acts both centrally and peripherally, its peripheral release is probably more important in the control of gut epithelial physiology.

In conclusion, this chapter has explored the particular functions of individual highly specialised cells within the gastrointestinal tract. The interplay of these cells with the enteric nervous system and the CNS enables normal motility and absorptive/secretory processes to take place, maintains the homeostasis of the gastrointestinal tract, and protects it from chemical or physical insults. Our increasing understanding of the neural connections and transmitters which regulate gut responses and maintain gut integrity should permit pharmacological manipulation of these responses in conditions where an imbalance is present.