Synaptic transmission in enteric circuits

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The enteric nervous system of the gastrointestinal tract is the largest and most complex nervous system in the body, outside the brain. It contains intrinsic sensory neurons (also known as intrinsic primary afferent neurons), several classes of interneurons, excitatory and inhibitory motor neurons supplying both the circular and longitudinal muscle layers, secretomotor neurons, vasodilator neurons and intestinofugal neurons. Each of these types of neurons can be subdivided into several different subtypes according to their projections and neurochemistry. Thus, there are probably at least 20 different subtypes of enteric neurons distributed between the two main ganglionated plexuses of this system, the myenteric and submucosal plexus.

Communication between enteric neurons has been studied in a variety of ways, but perhaps the most precise method has been *via* intracellular recordings that have focused on the myenteric and submucosal plexuses of the guinea-pig small intestine. These studies have revealed a wide variety of synaptic potentials in different classes of enteric neurons. The majority of neurons exhibit fast excitatory synaptic potentials (EPSPs) mediated by ionotropic receptors. In guinea-pig, mouse and human these are predominantly mediated by acetylcholine (ACh) acting on nicotinic ACh receptors, but there is evidence for fast EPSPs mediated by P2X purinoceptors in all three of these species. There is also evidence for fast EPSPs mediated by 5-HT3 receptors in both myenteric and submucosal neurons of the guinea-pig ileum, although whether they are present in other species and regions is less clear. Intrinsic sensory neurons typically lack fast EPSPs, but exhibit a variety of slow EPSPs mediated *via* metabotropic receptors, responses that are not usually thought to play a major role at central synapses. The best established transmitters mediating slow EPSPs in intrinsic sensory neurons are tachykinins acting *via* NK1 and NK3 tachykinin receptors and serotonin acting on 5-HT7 receptors. Interneurons and motor neurons also exhibit slow EPSPs that are mediated by a variety of different transmitter receptor combinations including tachykinins acting at NK1 and NK3 receptors, a purine acting on P2Y1 receptors and glutamate acting on metabotropic glutamate receptors of either the mGluR1 or the mGluR5 subtypes. Metabotropic transmission also accounts for inhibitory synaptic potentials mediated by noradrenaline action on α2-adrenoceptors, somatostatin acting on SST1 and SST2 receptors and possibly serotonin acting on 5-HT1A receptors. There is less convincing, but suggestive, evidence for roles for the primary neurotransmitters of the central nervous system, glutamate and γ-aminobutyric acid (GABA). However, it should be noted that GABA depolarizes a subset of enteric neurons, in contrast to its predominantly hyperpolarizing effect in the brain and spinal cord. In guinea-pig, GABA effects appear to be confined to intrinsic sensory neurons, but in mouse interneurons and motor neurons may also be affected.

While this rich variety of synaptic potentials and transmitters raises many possibilities, their precise functional roles have been difficult to determine. There are several reasons for this including inadequate pharmacological tools, the complexity of the circuits mediating different intestinal behaviours including propulsion, segmentation, receptive relaxation, retropulsion and water and electrolyte secretion plus the fact that many transmitter pathways differ subtly or markedly between different species. For example, transmission in descending inhibitory reflex pathways in the guinea-pig depends on purines acting at P2X and P2Y1 receptors with little involvement of ACh acting on nicotinic receptors, while in rat transmission in this pathway is entirely dependent on cholinergic transmission.

The problem is compounded by the absence of basic information about the molecular nature of synapses in the enteric nervous system, where well established components of central synapses have either not been identified or are not located where they may be expected to be. For example, synaptophysin and synaptotagmin-1 are synaptic vesicle proteins that are thought to mark a large proportion of nerve terminals in the brain, but these are largely located in many, but by no means all, cholinergic terminals in the enteric nervous system. Neither seems to be located in non-cholinergic enteric terminals, suggesting involvement of different release processes in the enteric nervous system.

Understanding the nature and specific functions of transmission in specific enteric neural circuits is essential for understanding gastrointestinal physiology and pathophysiology. Future studies using optogenetics and genetically encoded calcium indicators how great promise for answering these questions.