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Opioids, the Enteric Nervous System, and Postoperative Ileus

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Postoperative ileus, which is characterized by quiescence of the intestinal musculature, reflects the operation of a neural program in the enteric nervous system (ENS) in which the synapses that form the propulsive motor circuits are "locked" into an inactive state. In the inactive state, a component of the inhibitory motor innervation of the musculature remains active, and as a consequence, responsiveness of the muscle to electrical signals from pacemaker cells called interstitial cells of Cajal is suppressed. Physiological ileus is the normal absence of motility that occurs for varying lengths of time in different digestive states. Physiological motor quiescence becomes pathological when the synapses in the neural microcircuits for the motor programs in the ENS program library are rendered inoperative for abnormally long periods. In this state of paralytic ileus, the basic circuits are "locked" in an inactive state, while unremitting activity of inhibitory motor neurons continuously suppresses autogenic muscular activity. Release and actions of endogenous opioid peptides within the ENS inactivate the synaptic microcircuits and might account for the accompanying paralytic ileus. This hypothesis is based in part on the known actions of opioid peptides and opiates on the cellular neurophysiology of enteric neurons. The prototype opiate is morphine, which acts to delay gastric emptying and intestinal transit, to suppress intestinal secretion of water and electrolytes, and to suppress transport of bile into the duodenum—all of which are related to suppression of neuronal excitability and synaptic transmission in the ENS.
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Opiates are derivatives of opium that have been recognized, since the earliest beginnings of clinical pharmacology, as products isolated from poppy plants that effectively treat the watery stools of dysentery, relieve pain, and produce euphoria. Opioids are substances that have actions like those of opiates. Opiates produce their effects in the body by binding to receptors for endogenously released peptidergic neurotransmitters/neuromodulators, called opioid peptides, in both the central and peripheral nervous systems. Enkephalins, endorphins, and dynorphins are three distinct families of opioid peptides. Each is derived from a precursor polypeptide coded by one of three corresponding genes. Three primary opioid receptor types, μ-, δ-, and κ-receptors, mediate the actions of opiates and opioid peptides.

The effects of opiates and opioids on organ-level gastrointestinal functions reflect actions taking place to a major extent in both the enteric nervous system (ENS) and the central nervous system (CNS). Understanding the mechanisms of action of opiates and endogenously released opioid peptides at the organ level in the digestive tract requires insight into the ways in which they act at the various types of opioid receptors to alter neuronal excitability and neurotransmission in the ENS. Both positive therapeutic effects and pathophysiologically adverse effects of administration of opioid receptor agonists and antagonists on normal gut function are best understood in the context of the neurophysiology of the ENS and mechanisms of neural control of gastrointestinal smooth muscle, secretory glands, and blood-lymphatic vasculature. Moreover, understanding of postoperative ileus demands thorough grounding in the mechanisms by which the ENS programs gastrointestinal motility.

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Enteric Nervous System

The digestive tract does not work in the absence of the integrative functions of the ENS. Normal functioning of the neu-

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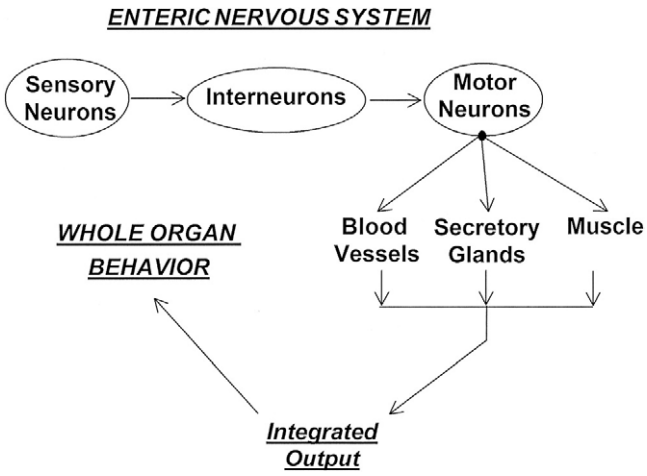

Figure 1 Heuristic model for the enteric nervous system (ENS). Sensory neurons, interneurons, and motor neurons are synaptically interconnected to form the integrated microcircuits of the ENS. Like the central nervous system, sensory neurons, interneurons, and motor neurons are connected synaptically for flow of information from sensory neurons to interneuronal integrative networks to motor neurons to effectors. The effector systems are the musculature, secretory glands, and blood vessels. The ENS organizes and coordinates the activity of each effector system into behavior of the whole organ that is adaptive for differing digestive states.

ral networks of the ENS is necessary for effective motility, secretion, and blood flow and for coordination of these functions into organized patterns of behavior at the level of the integrated organ.

The ENS is an independent integrative nervous system, which shares most of the properties of the central nervous system (CNS). It functions to integrate contraction of the musculature, glandular secretion, and intramural blood flow into organized patterns of digestive behavior. The neural networks of the ENS may either evoke contractions of the gut musculature or inhibit contractile activity as required for the organization of specific patterns of intestinal motility at any given time. They organize absorption from and secretion into the intestinal lumen and integrate these functions with motility. Minute-to-minute neurophysiological control of secretion and absorption maintains intraluminal osmolarity and pH at set points necessary for optimal digestion. Moreover, intramural blood flow and the distribution of flow to the musculature, mucosa, and lamina propria are controlled by the integrative microcircuitry of the ENS. As might be expected, malfunctions of integrative ENS control of the gut's effector systems are increasingly recognized as underlying factors in gastrointestinal disorders, including postoperative ileus.

The musculature, mucosal secretory glands, and blood and lymphatic vasculature are the gut's effector systems (Fig. 1). Moment-to-moment behavior in any of the specialized compartments of the gut (eg, stomach, small and large intestine) reflects neurally integrated activity of the effector systems. The ENS not only controls the activity of each effector, it coordinates the activity of each to achieve organized behavior of the whole organ. Coordinated activity is achieved through the timing of excitatory and/or inhibitory neural inputs to each effector system individually. Coordination of mucosal secretion and muscle contractile activity in a timed sequence during intestinal propulsion of luminal contents is an example of ENS integrative function. Secretion of H_2O, electrolytes, and mucus occurs first, followed by propulsive contractions taking place in the musculature.[1] A simultaneous increase in neurally controlled blood flow to the secretory glands supports the enhanced secretory response (Fig. 2).

The ENS is a "minibrain" with a library of programs for multiple forms of small or large intestinal behavior (see Fig. 1). A specific program determines the mixing pattern of motor behavior in the postprandial state, another establishes the pattern of interdigestive intestinal motility that characterizes the fasting state (ie, migrating motor complex), and still another acts in defense against infectious invaders, enterotoxins, and food allergins.[2] In general, the gut does not work without the ENS. Sphincters do not relax, organized propulsion does not occur, and liquidity of the luminal contents is disordered.

ENS Control of the Small and Large Intestine

Intestinal motility refers to wall movements or lack thereof in the small and large bowel. Integrated function of the musculature and nervous system is necessary for generation of the various patterns of motility that reflect operation of the various motor programs stored in the program library of the ENS (see Fig. 1). Intestinal motor movements involve the neurally controlled application of forces of muscle contraction to mix and propel material present in the lumen.

Intestinal Musculature

The physiological properties of the intestinal musculature dictate the kind of neural control required for adequate generation of specialized patterns of motility. The musculature is unitary type smooth muscle. Unitary type smooth muscles are autogenic; they contract spontaneously in the absence of neural or endocrine influence and contract in response to stretch. The muscle fibers in unitary type smooth muscles are connected to their neighbors by gap junctions.[3] Gap junctions are permeable to ions and transmit ionic electrical current from muscle fiber to muscle fiber. This electrical connectivity accounts for the electrical syncytial properties of unitary type smooth muscle. Gap junctions confer electrical behavior analogous to that of cardiac muscle and account for the spread of action potentials and accompanying myogenic contractions from points of initiation (eg, pacemaker regions) in three dimensions from muscle fiber to muscle fiber within the bulk of the muscle.[4]

Networks of specialized pacemaker cells, called interstitial cells of Cajal (ICCs), are associated with the intestinal smooth musculature.[5] Pacemaker potentials (ie, electrical slow waves) originate in the ICC networks and appear as rhythmic