Chapter 17
Enteric Neurobiology: Discoveries and Directions

Jackie D. Wood

NANC Hypothesis

The noncholinergic, nonadrenergic hypothesis (NANC hypothesis), espoused by Geoffrey Burnstock in Australia was a giant step forward in understanding of gastrointestinal motility and for neurogenic secretion (Fig. 17.1). It emerged in 1964 when he, Graham Campbell and Michael Bennett, at the University of Melbourne, together with Mollie Holman at Monash University, reported that inhibitory responses to sympathetic nerve stimulation were blocked by bretylium and guanethidine; whereas, a strong inhibitory component of transmural electrical stimulation was unaffected by these agents (Burnstock et al. 1964). This suggested that the inhibitory neurotransmitter was not a catecholamine and led to Burnstock's canonical hypothesis that the transmitter was a purine nucleotide (Burnstock 1972). Existence of the NANC neurons is revealed during transmural electrical field stimulation as inhibition of ongoing muscular electrical and contractile activity, followed by postinhibitory rebound excitation at the offset of stimulation (Fig. 17.1a). Removal of ganglion cell bodies from the myenteric plexus of a strip of guinea pig taenia coli eliminated inhibitory junction potentials that could normally be evoked by nicotinic agonists (Burnstock et al. 1966). Thereby, reinforcing the hypothesis that the NANC inhibitory musculomotor neurons were in the myenteric plexus.

Subsequent workers found that subpopulations of NANC inhibitory musculomotor neurons were firing spontaneously and that a major function in the intestine was continuous suppression of the autogenous activity of the unitary type smooth musculature of the circular muscle coat. Enteric neurons in multiple species were found to fire continuously (Wood 1970, 1973; Ohkawa and Prosser 1972;

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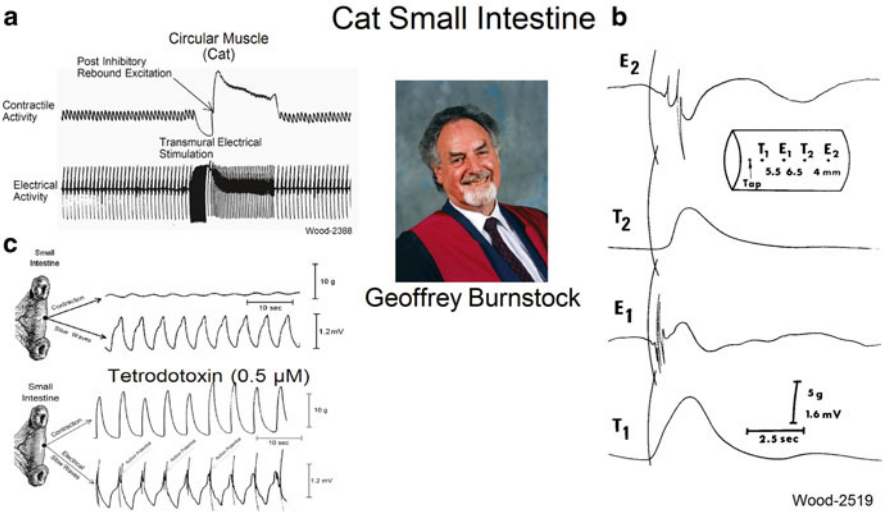

Fig. 17.1 Significance of Burnstock nonadrenergic-noncholinegic (NANC) inhibitory musculomotor neurons. (**a**) Inhibition of ongoing electrical and contractile activity and post inhibitory rebound excitation in the circular muscle coat in response to transmural electrical stimulation. (**b**) Records from 2 force transducers (T_1 and T_2) and 2 electrodes (E_1 and E_2) of propagated muscle action potentials and associated contractions evoked by a mechanical stimulus (tap) in the presence of ENS neural blockade by tetrodotoxin. Blockade of NANC neurons permitted propagation of the action potential in the aboral direction in the electrical syncytium throughout the length preparation. (**c**) Electrical slow waves have no action potentials at their crests and evoke only small amplitude contractions when NANC neurons are firing spontaneously in the upper two traces. Blockade of ongoing NANC firing by tetrodotoxin results in the appearance of muscle action potentials and large amplitude contractions associated with each slow wave (Wood 1972; Wood and Marsh 1973)

Nozdrachev et al. 1975). In intestinal segments in vitro, when firing was prevalent, muscle action potentials and associated contractile activity were absent. However, myogenic electrical slow waves were always present. Blockade of firing by tetrodotoxin resulted in every cycle of the electrical slow waves triggering intense discharge of muscle action potentials and large amplitude contractions (Fig. 17.1c) (Wood 1970, 1972; Ohkawa and Prosser 1972; Wood and Harris 1972; Wood and Marsh 1973; Biber and Fara 1973; Tonini et al. 1974; Bortoff and Muller 1975). When firing of the NANC inhibitory motor neurons was ongoing, neither mechanical stimulation nor transmural electrical stimulation effectively elicited contractile responses of the intestinal circular musculature (Wood 1972; Wood and Perkins 1970). Following neuronal blockade, both electrical and mechanical stimulation readily triggered muscle action potentials and waves of contractile activity that were propagated for extended distances in either direction along the longitudinal axis of an intestinal segment (Fig. 17.1b) (Wood 1972; Wood and Perkins 1970).

Various specialized patterns of intestinal motility are dependent upon integrated disinhibition of the intestinal circular muscle coat, which owing to interfiber gap junctions, behaves as a functional electrical syncytium activated by electrical slow

wave pacemaker potentials. In the normally functioning bowel, integrative control of the activity of NANC inhibitory neurons determines; (1) whether a particular cycle of an electrical slow wave triggers a response in the circular muscle; (2) the force of the contractile response triggered by a slow wave; (3) distance over which a muscle action potential and its associated contraction spreads from muscle fiber to fiber within the electrical syncytium; (4) the direction of spread of action potentials and associated contractions within the syncytium along a segment, which can be in the oral or aboral direction according to the motility pattern (see Fig. 17.5).

Enteric Neuronal Electrophysiology

Following in the wake of the NANC hypothesis, major progress in the neurobiology of the enteric nervous system (ENS) came from microelectrode recording of electrical behavior of single neurons. I published, in 1970, records of single unit activity of neurons in the myenteric plexus of the cat that were immediately confirmed by Ohkawa and Prosser in the United States and AD Nozdrachev and associates in Russia (Wood 1970; Ohkawa and Prosser 1972). Research on the cellular neurophysiology of ENS neurons gained significant momentum with reports of results of intracellular recording, with "sharp" microelectrodes describing electrical and synaptic behavior in guinea pig ENS neurons (Hirst et al. 1974; Nishi and North 1973; Wood and Mayer 1978a). Two types of ENS neurons were identified based on their electrophysiological and synaptic behavior and named either AH-type 2 or S-type 1 neurons (Fig. 17.2). The names were an arbitrary combination of terms that recognized G. David Hirst, who was working in the Department of Physiology, Monash University, Clayton, Victoria, Australia and R. Allan North working first as a student in the Department of Pharmacology, University of Aberdeen, Aberdeen, Scotland, UK and later as a postdoctoral fellow in the Neurophysiology Laboratory, Department of Pharmacology, Loyola University Medical Center in Maywood, Illinois, USA as the first to describe the two kinds of neurons (Hirst et al. 1974; Nishi and North 1973). The names combined the alphabetical terms used by Hirst and numerical designations used by North. The terms are facilitating because AH-type 2 neurons usually have Dogiel Type 2 multipolar morphology and S type 1 neurons generally are unipolar like Dogiel Type I neurons (Fig. 17.2).

Also taking place in this heyday for ENS neuronal electrophysiology was the discovery of slow excitatory postsynaptic potentials (Slow EPSPs) which hitherto was unknown elsewhere in the nervous system (Wood and Mayer 1978b; Katayama and North 1978). Inhibitory sympathetic noradrenergic synaptic transmission was also discovered at this time (Hirst and McKirdy 1975; North and Surprenant 1985). The competitive nature of ENS research at the time was exposed when the group of R. Alan North published evidence that slow EPSPs were mediated by substance P and Jackie Wood's group was resolute that serotonin was the neurotransmitter (Wood and Mayer 1978b; Katayama and North 1978; Grafe et al. 1979). As it played out, both were right.

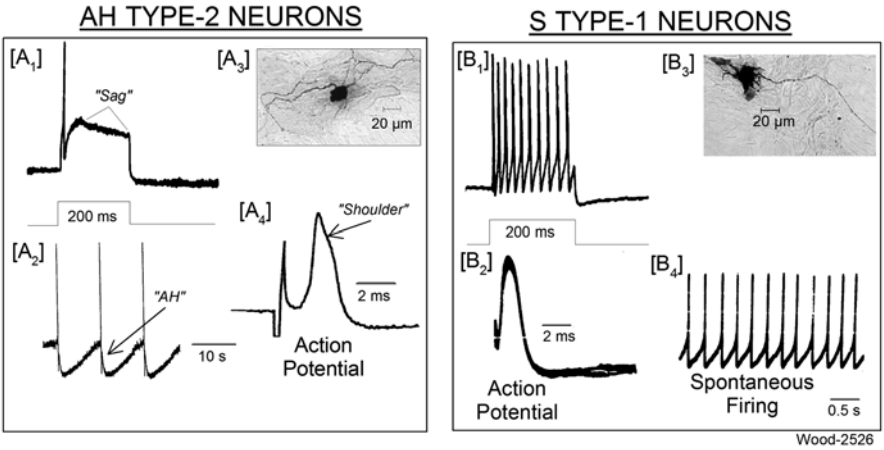

Fig. 17.2 AH type-2 and S type-1 ENS neurons, first described by Hirst et al. (1974) and Nishi and North (1973) are distinguished by specific electrophysiological behavior. (A_1) Intraneuronal injection of a 200 ms depolarizing current pulse could evoke only a single action potential, regardless of the strength of the depolarizing pulse. Neuronal excitability in AH neurons is low and membrane depolarization evokes none or only one or two action potentials at the onset of a depolarizing current pulse. The action potential is followed by a "sag" in the electrotonic potential, which reflects an increase in ionic conductance. (A_2) A long-lasting after hyperpolarization (AH) is associated with the action potentials in AH type-2 neurons. (A_3) Multipolar morphology of the AH Dogiel Type II neuron from which the records were obtained as revealed by intraneuronal injection of the marker, biocytin, from the microelectrode. (A_4) A "shoulder" on the falling phase of the action potential reflects opening of voltage-gated Ca^{2+} channels. (B_1) S type-1 ENS neurons are more excitable that AH neurons and fire repetitively during intraneuronal injection of depolarizing current pulses with the firing frequency increasing in direct relation to the strength of membrane depolarization. (B_2) Unlike AH neurons, S type-1 neurons have no "shoulder" on the action potentials. (B_3) Morphology of the uniaxonal neuron from which the records were obtained. (B_4) Unlike AH neurons, S type-1 neurons fire spontaneously, with each action potential preceded by a ramp-like prepotential

Slowly-activating membrane depolarization, which continues for several seconds to minutes and sometimes hours after termination of stimulation and release of the neurotransmitter from the presynaptic terminal, was found to be a major characteristic of slow EPSPs (Fig. 17.3). Excitatory mediators released in paracrine fashion from enteric mast cells, and other inflammatory/immune cells were found to also evoke slow EPSP-like responses (Frieling et al. 1994a, b; Liu et al. 2003a). Slow inhibitory postsynaptic potentials (IPSPs), reported at the time by Hirst and McKirdy (1975) and the partnership of North and Surprenant (1985), were described as hyperpolarizing synaptic potentials found in both myenteric and submucosal ganglion cell somas. IPSPs are now known to be more common in the submucosal than in the myenteric plexus. In the submucosal plexus, they were found to be mediated by norepinephrine release from sympathetic postganglionic neurons and predominate in the non-cholinergic secretomotor/vasodilator neurons that release vasoactive intestinal peptide at junctions with secretory glands in the mucosa (North and Surprenant 1985; Bornstein et al. 1988).

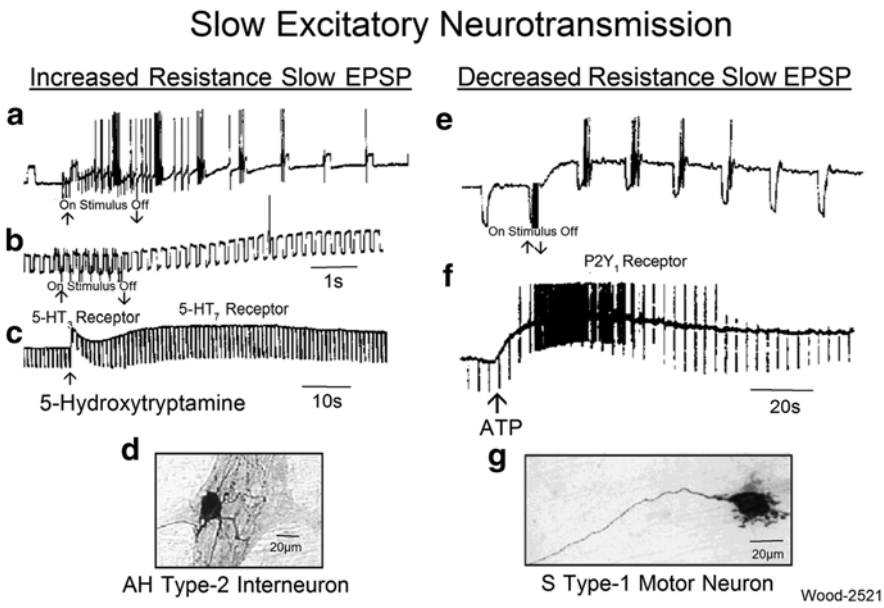

Fig. 17.3 Two kinds of slow excitatory postsynaptic potentials (EPSPs) are identified by changes in membrane conductance (i.e., input resistance) during the depolarization phase. (**a**) Slow EPSPs in AH type-2 ENS neurons are characterized by long-lasting membrane depolarization, suppression of the AH and associated elevation of excitability that continues for extended periods after termination stimulus-evoked transmitter release. (**b**) Input resistance increases during the depolarization phase of slow EPSPs in AH type-2 ENS neurons. Downward deflections are electrotonic potentials evoked by repetitive intraneuronal injection of constant-current hyperpolarizing pulses. Increased amplitude of electrotonic potentials reflects closing of ionic channels (i.e., increased input resistance). (**c**) Application of 5-hydroxytryptamine by pressure microejection from fine tipped pipettes evokes two kinds of slow EPSPs in the same AH type-2 ENS neurons. One kind evoked by stimulation of the 5-HT_3 receptor subtype is associated with a decrease in input resistance; a second kind evoked by the 5-HT_7 receptor subtype is associated with increased input resistance. (**d**) Multipolar morphology of the AH Dogiel Type II neuron from which the records were obtained. (**e**) Slow EPSPs in S type-1 neurons are characterized by long-lasting membrane depolarization associated with elevated excitability and increased membrane conductance reflected by increased input resistance. (**f**) Application of ATP by pressure microejection from fine tipped pipettes evokes slow EPSP-like excitation mediated $P2Y_1$ receptors in S type-1 ENS neurons. (**g**) Morphology of the uniaxonal neuron from which the records were obtained

Neurochemical Coding of Enteric Neurons

Application of emerging immunohistochemical and projection methodologies in parallel with the electrophysiological work, which was moving forward at the same time in Australia, was responsible for major expansion of insight in the rapidly developing importance and recognition of ENS neurobiology in the late 1980s and 1990s. Marcello Costa and John Furness working at Flinders University, and Furness, later working at the University of Melbourne, were the pioneers in major

progressive steps that established the concept of chemical coding for functional identification of neurons in the ENS synaptic networks. Their two books continue to be mandatory reading for anyone working in the ENS (Furness and Costa 1987; Furness 2006). Immunohistochemical approaches became underpinning, in concert with intraneuronal marking during electrophysiological recording, for numerous studies by others of the cellular neurobiology of the kinds of neurons comprising the synaptic microcircuits in the ENS and continues at this writing.

Inflammation

Discoveries in the 1980s–1990s that inflammatory-immune cells communicate in paracrine fashion with the ENS set the stage for understanding motility and secretory pathophysiology in food allergies, infectious enteritis, radiation induced enteritis, idiopathic enteritis (e.g., ulcerative colitis), as well as, stress-evoked events in functional gastrointestinal disorders (e.g., irritable bowel syndrome) (Hu et al. 2003; Wood 2004, 2007a, b, 2012; Tamura and Wood 1992; Liu et al. 2003b). Examples include demonstrations that AH-type neuronal electrophysiology in states of mucosal inflammation, induced by instillation of toxic chemicals, exhibit persistent enhanced excitability (Hoffman et al. 2011; Krauter et al. 2007; Linden et al. 2003; Lomax et al. 2006, 2007; Mawe et al. 2009). Enhanced excitability in these cases mimics the excitatory paracrine actions of several different mast cell mediators to augment excitability by suppressing the postspike after-hyperpolarization of AH-type neurons and increasing their input resistance (Frieling et al. 1994a; Tamura and Wood 1992; Liu et al. 2003b; Gao et al. 2002; Nemeth et al. 1984; Starodub and Wood 2000a, b).

Hardwired Polysynaptic Propulsive Motor Circuit

Bayliss and Starling's (1899) discovery that local intestinal stimulation evokes inhibition below the point of stimulation and excitation above it in association with a wave of circular muscle contraction traveling in the aboral direction ushered in ENS neurobiology. Although referred to as "the peristaltic reflex" over subsequent years; whether reflex is appropriate in the Sherringtonian sense has been opened to question (Wood 2008). On the other hand, there is little question that a hardwired polysynaptic reflex circuit at a low to intermediate level of neural organization in the ENS underlies the propulsive motility patterns in the small and large intestine and esophagus. The circuit for propulsion in the direction of the anus is "wired" in such a way that it evokes relaxation of the circumferentially oriented muscle layer and contraction of the longitudinal muscle below the initiation area and contraction of the circumferentially oriented muscle layer above the initiation site (Fig. 17.4A, B). The "wiring" is reversed for propulsive motility moving luminal contents in the oral

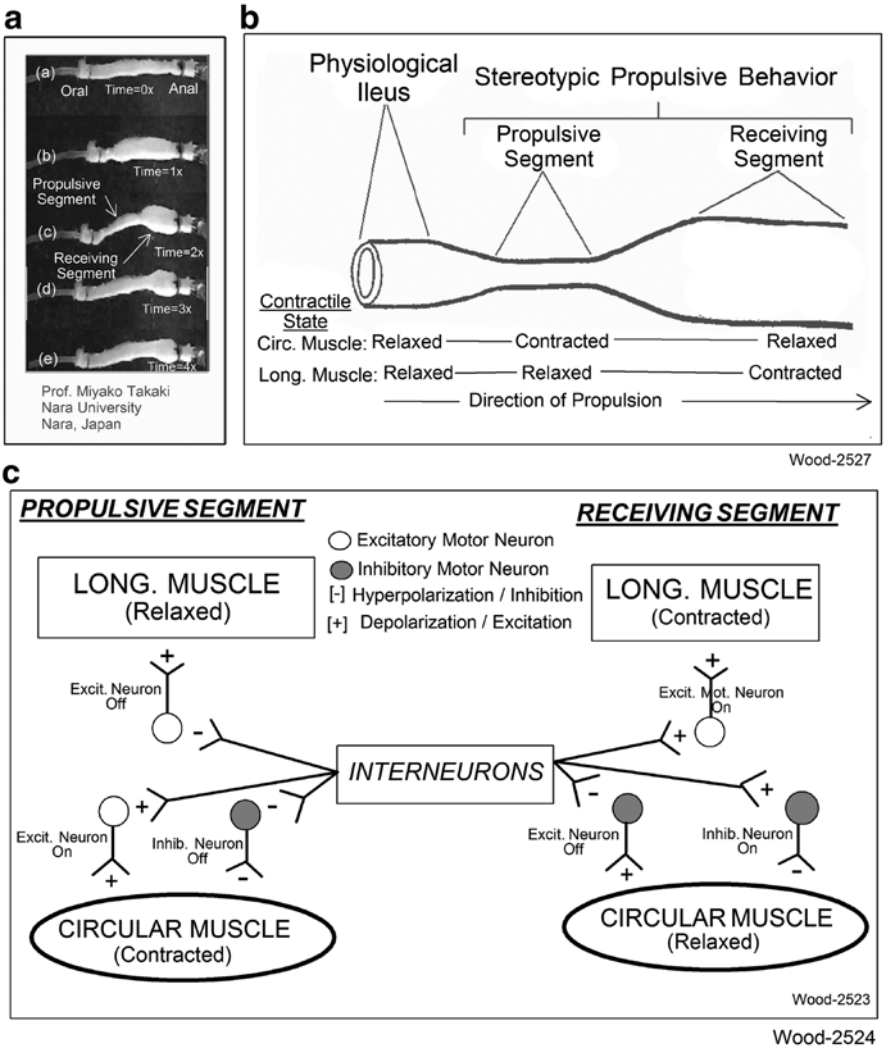

Fig. 17.4 A "hardwired" polysynaptic peristaltic reflex circuit in the ENS underlies integrated control of intestinal and esophageal propulsive motility. (**A**) Motor behavior of the intestinal wall during propulsive motility in a segment of guinea-pig ileum in response to distension by infusion of physiological saline through a catheter tied into the oral end. (*a*) Time = 0×. (*b*) With time advanced to 1×, shortening of the segment due to contraction of the longitudinal muscle coat and inhibition of the circular muscle coat expands the lumen into a receiving segment. (*c*) With time advanced to 2×, reduction in the diameter and lengthening of the propulsive segment occurs as the circular muscle coat contracts. Also at time = 2× expansion of the lumen of the receiving segment occurs as the longitudinal muscle coat contracts and the circular muscle is relaxed by firing of inhibitory musculomotor neurons. (*d–e*) Propulsive motility continues to empty the segment at time = 3–4×. Redrawn from video images kindly provided my Prof. Miyako Takaki. (**B**) In a heuristic model for propulsive motility, the circumferential and longitudinal muscle layers of the intestine behave in a stereotypical pattern to propel luminal contents. A "hardwired" polysynaptic circuit in the ENS determines the pattern of behavior of the two muscle layers. During propulsion, the longitudinal muscle coat in the segment ahead of the advancing intraluminal contents contracts while the circumferential muscle layer relaxes simultaneously. Simultaneous shortening of the longitudinal intestinal axis and relaxation of the circumferential muscle in the same segment

direction during emesis in the small intestine. For emetic propulsion, the circuit is "wired" such that it evokes relaxation of the circumferentially oriented muscle layer and contraction of the longitudinal muscle in the direction of the stomach and contraction of the circumferentially oriented muscle layer as the trailing event. Like spinal motor reflexes, sequencing of the behavior of the intestinal longitudinal and circular muscles is hardwired into the circuitry, which ensures that the propulsive motor behavior is repeated stereotypically in every occurrence (Fig. 17.4B). Propulsion of the luminal contents is determined by the sequence in which the hardwired circuit activates excitatory and inhibitory musculomotor neurons to the longitudinal and circular muscle layers. During propulsion, the longitudinal muscle coat in the segment ahead of the advancing intraluminal contents contracts in response to activation of its excitatory motor innervation, while at the same time, the circular muscle layer relaxes in response to activation of its NANC inhibitory motor innervation (Fig. 17.4A). The esophagus and intestine behave geometrically like a cylinder with constant surface area. Therefore, a reduction in radius of the cylinder during contraction of the circular muscle is accompanied by a lengthening of the segment as can be seen in Fig. 17.4A (Wood and Perkins 1970). On the other hand, shortening of the longitudinal axis of the segment, during contraction of the longitudinal muscle coat, is accompanied by a widening of the cross-sectional diameter as seen in Fig. 17.4A. Simultaneous shortening of the longitudinal axis in concert with inhibitory relaxation of the circular muscle coat results in expansion of the lumen, which prepares a receiving segment for the forward-moving intraluminal contents during activation of the hardwired propulsive motor circuit. A propulsive segment is formed behind the receiving segment when synaptic connections in the circuit "turn off" the inhibitory musculomotor innervation to the circular muscle. Silencing of the inhibitory innervation permits electrotonic spread of electrical slow wave current into the circular muscle, depolarization of the muscle fibers to action potential threshold and action potential-evoked contraction of the circular muscle in the propulsive segment.

Contractions recorded by sensing devices implanted on the bowel during digestive and interdigestive small intestinal motor behavior reflect the formation of propulsive segments (see Fig. 17.5). They occur at the frequency of the electrical slow waves because removal of inhibition from the circular muscle allows it to respond to the electrical current flowing from networks of interstitial cells of Cajal during

Fig. 17.4 (continued) results in expansion of the lumen, which becomes a receiving segment for the forward moving contents. The allied function in the circuit is contraction of the circular muscle in the segment behind the advancing intraluminal contents. The longitudinal muscle layer in the same segment relaxes simultaneously with contraction of the circular muscle, which results in conversion of this region to a propulsive segment that propels the luminal contents ahead into the receiving segment. (**C**) Heuristic model for a "hardwired" polysynaptic propulsive motor circuit in the ENS. When the circuit is active, excitatory motor neurons to the longitudinal muscle coat and inhibitory motor neurons to the circular muscle coat are firing to form the receiving segment below the point of stimulation. At the same time firing of excitatory motor neurons to the circular muscle coat and inactivation of inhibitory motor neurons to the circular muscle coat occurs in the propulsive segment above the point of initiation

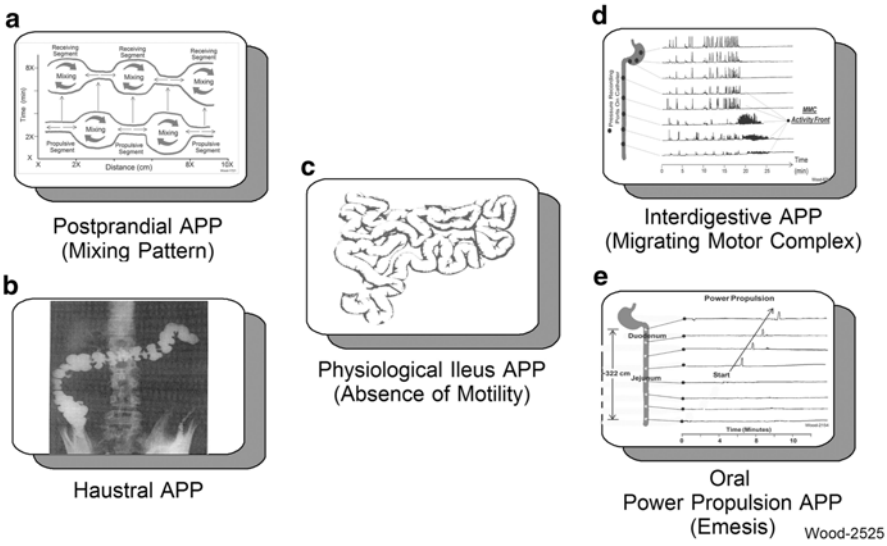

Fig. 17.5 The enteric nervous system can be viewed, heuristically, as a "minibrain" with a library of applications, like digitally programed "apps", for multiple patterns of small or large intestinal behavior. (**a**) A specific app determines motor behavior in the postprandial state. (**b**) A haustral app programs for formation of haustra in the colon. (**c**) Running of a physiological ileus app programs for a quiescent bowel. (**d**) Another app establishes the pattern of intestinal motility, called the migrating motor complex, which characterizes the fasting state. (**e**) The specialized motility pattern that occurs in the upper one-third of the small intestine during emesis reflects output of another of the apps in the library. During emesis, peristaltic propulsion in the upper one-third of the small intestine is reversed for rapid movement of the luminal contents toward the stomach

each slow wave cycle. On the other hand, formation of the propulsive segment during power propulsion occurs unrelated to the frequency of the electrical slow waves and involves much stronger contraction of the circular muscle in the propulsive segment than occurs during peristaltic propulsion in the digestive and interdigestive motor patterns (see Fig. 17.5).

Central Pattern Generators

As might be expected for an independent integrative nervous, such as the ENS, evidence has accumulated to suggest that central pattern generators are expressed at higher levels of neurophysiological organization in the ENS. Central pattern generators (CPGs) are circuits in nervous systems that generate repetitive patterns of motor behavior independent of sensory input. CPGs underlie rhythmic motor behaviors such as walking, chewing, swimming, feeding, flying and respiration in vertebrates and invertebrates (Lomax et al. 2007; Mawe et al. 2009; Gao et al. 2002; Nemeth et al. 1984; Starodub and Wood 2000a, b; Bucher et al. 2006; Marder 2000,

2001; Marder and Bucher 2001; Marder et al. 2005; Marder and Rehm 2005). Rhythmic and cyclical motor and secretory behaviors in the intestinal tract are most likely reflections of the output one or more CPGs at higher levels of ENS organization.

CPGs have three properties in common: (1) motor output patterns consist of rhythmically timed bursts of action potentials that arise either from an ensemble of neurons that can't be traced to any individual neuron in the system or are generated by endogenous firing of a single neuron; (2) stereotypic sequences of repetitive behavior (e.g., walking) are initiated by activation of single "command neurons" or by an overlay of a paracrine neuromodulator on the CPG circuit; (3) motor behavior can be initiated and modified by sensory feedback, but the stereotyped sequence of motor events continues in the absence of sensory input.

Electrophysiological results suggest that CPGs in the ENS have endogenous neuronal oscillators that determine the timing of recurrent firing of ENS musculomotor and secretomotor neurons (Wood 1970; Wood and Mayer 1973). This is evident, in single unit records, for a subset of neurons in stretched intestinal whole-mount preparations from guinea pig, dog and cat small intestine in vitro. The putative CPG neurons fire bursts of action potentials continuously over long time periods with the spike bursts fired precisely at 6-s intervals or at exact multiples of 6 s (i.e., 12, 18, or 24 s) for the cat small intestine. Blockade of synaptic transmission does not change the timing of the discharge, which is expected if the CPGs are endogenous "clocks" (Wood 1975, 2008; Athey et al. 1981).

A response to paracrine release of histamine from inflammatory/immune cells is an example of how a neuromodulator influences a circuit with a CPG in the ENS to generate a rhythmic pattern of glandular secretion linked with motility. Application of histamine to simulate degranulation of enteric mast cells or actual degranulation of mast cells in the intestine of antigen-sensitized animal models in vitro evokes rhythmic cycles of chloride secretion with the peak of each cycle linked to a contraction of the circular muscle coat (Frieling et al. 1993, 1994a, b; Wang and Cooke 1990). The secretory cycles occur at about 1 per min in the guinea pig colon. As each secretory cycle peaks, contraction of the muscularis externa occurs (Cooke et al. 1993). Activation of the CPG in this case is independent of the concentration of the neuromodulator with the exception of requirement for a threshold concentration. The integrated neural network at this level of organization behaves like it incorporates a "switch" that activates the neural program, including the CPG, in on-off manner.

Neuromodulatory action of histamine to activate an ENS behavioral program that incorporates a CPG reminds of a similar neuromodulatory action of the enteroendocrine hormone, cholecystokinin in the small intestine. Application of cholecystokinin, to mimic enteroendocrine release in the cat small intestine, activates in all-or-none manner a neural program for repetitive cycles of propulsive motility (Weems et al. 1985). A comparable repetitive patterning of activation of the "hard-wired" ENS propulsive reflex circuit at a CPG-level of organization continues when flat sheet preparations from guinea pig colon remain tightly stretched for periods of minutes in vitro (Spencer et al. 2001; Spencer and Smith 2004).

Program Library

The ENS can be viewed as a "minibrain", which at a higher level of neurophysiological organization expresses a library of programs for multiple patterns of small or large intestinal behavior that call to mind the digitally programed "apps" in the Apple® Inc. app store. In this context, a specific app determines adaptive musculomotor behavior in the postprandial state and another establishes an adaptive pattern of intestinal motility that characterizes the fasting state. The specialized motility pattern that occurs in the upper one-third of the small intestine, during emesis, appears to reflect output of another of the Apps in the library. During emesis, propulsion in the upper one-third of the small intestine is reversed for rapid movement of the luminal contents over extended distances toward the stomach. The "emetic app" can be "called-up" from the library either by commands from the brain (e.g., emetic action of apomorphine) or by local sensory detection of threatening substances in the lumen (e.g., cupric sulfate). Still another app, referred to as *power propulsion* is "called-up" for defense against infectious invaders, enterotoxins or food allergins, as well as being the app for reverse propulsion during emesis. The ENS library in the small intestine behaves like it might have apps for at least 6 different patterns of motility (see Fig. 17.5). These motility apps are: (1) an interdigestive App; (2) a postprandial App; (3) an aboral power propulsion App; (4) emetic oral power propulsion App; (5) haustral app in the colon; (6) physiological ileus app (Fig. 17.5).

The postprandial app, in the small bowel, starts to run with the intake of a meal (Fig. 17.5a). It programs for a mixing pattern of motor behavior. Repetitive propulsive contractions of the circular muscle, which propagate only short distances, account for the segmentation appearance when the app is running (Fig. 17.5a). Circular muscle contractions in short propulsive segments are separated on either side by receiving chambers with relaxed circular muscle and contracting longitudinal muscle, each of which reflect activation of short "blocks" of the hardwired polysynaptic propulsive circuit in Fig. 17.4B. This mixing activity continues at closely spaced sites along most of the length of the small intestine so long as nutrients are present in the lumen.

The interdigestive app programs the migrating motor complex (MMC), which is the small intestinal motility pattern of the interdigestive state. It replaces the postprandial app after digestion and absorption of nutrients is complete 2–3 h after a meal in humans. Sensors attached to the stomach show the MMC starting as large amplitude contractions at 3 per minute in human distal stomach. Activity starts in the antrum and then migrates in the aboral direction into the duodenum and on through the small intestine to the ileum. When this app is "running" the MMC occupies a limited length of intestine called the activity front, which has an upper and a lower boundary (Fig. 17.5d). The activity front slowly advances, "migrates", down the intestine at a rate that progressively slows as it approaches the ileum. Propulsion of luminal contents in the aboral direction occurs, at electrical slow wave frequency, between the oral and aboral boundaries of the activity front. The circular muscle

contractions seen in the activity front are a reflection of the formation of the propulsive component of the hard-wired propulsive reflex circuit (Fig. 17.4A, B). Each propulsive wave traveling downward in the activity front consists of a propulsive and receiving segment (Fig. 17.4A). Successive propulsive waves start at the oral boundary and propagate to the aboral boundary of the activity front where they stop. Successive propulsive complexes start on average a short distance further in the aboral direction and propagate on average slightly beyond the boundary where the previous one stopped. Thus, the entire activity front slowly migrates down the intestine, "sweeping" the lumen clean as it goes. Running of this app inspired C.F. Code of the Mayo Clinic to name the MMC "the bowel's housekeeper" (Code 1979; Code and Marlett 1975). Physiological ileus is in effect along the bowel oral and aboral to the upper and lower boundaries of the migrating activity front. Neither MMCs nor physiological ileus can be seen in the small intestine in the absence of the ENS.

The power propulsion app programs rapid emptying of the contents of long segments of bowel. Power propulsive motility is characterized by strong, long-lasting contractions of the circular muscle that can travel over long distances along the small or large intestine. The contractions, when recorded by sensors, reflect formation of the propulsive segment of the hard-wired polysynaptic circuit in Fig. 17.4B and are sometimes referred to as "giant migrating contractions" because they are considerably stronger than the phasic contractions of the circular muscle coat that appear in the activity front of the MMC and in the mixing motility pattern (Sarna 1987). Giant migrating contractions have long durations of 18–20 s. They constitute the propulsive segment of the hardwired propulsive circuit in Fig. 17.4A and underlie efficient propulsive motility that strips the lumen clean as they travel at about 1 cm/s over long lengths of intestine. Motility programed by power propulsion apps differs from propulsive motility in the activity front of the MMC app and in the short-segment mixing seen when the postprandial app is running. The circular contractions in the propulsive segment are much stronger, occur independent of electrical slow waves and propagation takes place over much longer stretches of intestine.

Running of the power propulsion app rapidly moves the luminal contents of the distal small intestine or the large intestine in the anal direction. Noxious mucosal stimulation is the trigger for calling-up this app and closing any other app that might be running. Cramping pain, fecal urgency and diarrhea are associated with this motor behavior (Kamath et al. 1990). Exposure of the mucosa to irritants, introduction of luminal parasites, enterotoxins from pathogenic bacteria, allergic reactions, and exposure to ionizing radiation can start the aboral power propulsion app. Characteristics of this nature suggest that this app is a defensive adaptation for rapid clearance of threats from the intestinal lumen (Wood 2004).

The aboral power propulsion app appears as if it integrates as part of a more highly organized defensive app that is called-up by exposure to neuromodulators released during degranulation of enteric mast cells (Wood 2007a, 2012). Reconfiguration of the synaptic networks by an overlay of mast mediators integrates output of a secretomotor app with output of the power propulsion app in a timed

sequence. The secretomotor app runs first and evokes massive mucosal secretion of electrolytes and H_2O that "flushes" threats (e.g., microorganisms, allergins, noxious substances, etc.) into the lumen and maintains them in suspension in the lumen. The secretomotor response is followed immediately by running of power propulsion in the anal direction. Power propulsion rapidly propels the large volume of luminal liquid toward the anus. Arrival of the large volume in the recto-sigmoid region causes rapid distension, which triggers the ENS recto-anal reflex and relaxation of the smooth muscle of the internal anal sphincter. Opening of the internal sphincter, in this situation, underlies sensations of fecal urgency and emotional anxiety because the only remaining protection against incontinence is spinal-evoked contraction of the skeletal muscle of the puborectalis and external anal sphincter. Cramping abdominal pain is a hallmark of the large amplitude propulsive contractions evoked during power propulsion (Kamath et al. 1990). Symptoms of acute, explosive watery diarrhea are self-explanatory at this point.

The emesis app programs the specialized motility pattern that occurs in the upper one-third of the small intestine during emesis (Fig. 17.5e). During emesis, the direction of propulsive motility in the upper one-third of the small intestine is reversed for rapid movement of the luminal contents toward the stomach. As mentioned earlier, the emetic app can be called-up from the library either by commands from the brain or by local sensory detection of threatening substances in the lumen. Like the power propulsion app in the distal small intestine and in the large intestine, the adaptive significance of the emesis app is rapid removal of a threat from the lumen of the upper small bowel.

The physiological ileus app programs for quiescence of the autogenic intestinal smooth muscle (Fig. 17.5c). In clinical terms, ileus refers to forms of mechanical bowl obstruction that can be "dynamic" or "adynamic". Adynamic ileus is pathological obstruction of the bowel due to failure of the smooth muscle to contract. Dynamic ileus is pathological intestinal obstruction due to spastic contraction (i.e., failure to relax) of the circular musculature in a segment of bowel. Mechanical obstruction and adynamic and dynamic ileus are accompanied by severe colicky pain, abdominal distension, vomiting and constipation (Glasgow and Mulvihill 2002). Physiological ileus was suggested as a useful term in reference to non-pathological absence of motility in the small and large intestine (Grundy et al. 2006). It is a normal state of the bowel in which an app in the ENS programs quiescence of motor function. Physiological ileus disappears in the aganglionic segment of Hirschsprung's disease and after destruction or neuronal blockade in the ENS (e.g., treatment with nerve-blocking agents, such as tetrodotoxin). Disorganized and non-propulsive contractile behavior occur continuously (i.e., dynamic ileus) due to the autogenic contractile properties of unitary type smooth muscle when NANC inhibitory musculomotor neurons are blocked or destroyed by pathological processes, such as occur in neuropathic chronic intestinal pseudoobstruction or autoimmune neuropathy in functional gastrointestinal disorders (Wood et al. 2012; Stanghellini et al. 1987).

Looking Ahead

The ENS, like all other independent integrative nervous systems, whether in vertebrates or invertebrates is organized in a hierarchy of structures and functions ranging from the cellular-molecular at the lower tiers to plasticity in programmable synaptic networks ("apps") at the uppermost tiers. ENS neurobiology of the future is likely to continue its forward momentum with research oriented to opening the doors into the higher order functions in integrated synaptic microcircuits that include central pattern generators, program libraries reminiscent of Apple® apps and neuromodulatory reconfiguration of the outputs of hardwired synaptic circuits. Behavioral output properties will emerge at the uppermost tiers that will be unpredicted by complete knowledge of lower tiers. Understanding the uppermost tiers is a challenging but not formidable "brick wall" for the present generation's ENS research. Present and future generations of investigators must confront the need for innovation and application of advanced technologies in order to continue the efforts of past generations to break further through the "brick" wall.

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