Обзоры

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Autonomic brain in the gut

J. D. Wood✉[1]

[1] The Ohio State University College of Medicine Columbus, 304 Hamilton Hall, 1645 Neil Avenue, Columbus, OH 43210, USA

Author
Jackie D. Wood,
Scopus AuthorID: 35571627800,
e-mail: Jackie.wood@osumc.edu

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Abstract. The enteric nervous system (ENS) is an autonomic "brain-in-the-gut" that integrates gastrointestinal motility, secretion and blood flow into homeostatic patterns of gut behavior**.** Experimental models for the ENS are the same as for all independent integrative nervous systems, whether in the vertebrate brain and spinal cord or in invertebrate animals. The ENS coordinates and organizes the behavior of the musculature, secretory glands and vascular system, in each of the specialized organs of the gastrointestinal tract, into meaningful behavior of each organ. The ENS stores a library of programs for differing patterns of small and large intestinal adaptive behaviors. Programs in the library are akin to 21st century digital "apps" that run on smart phones, tablet computers and comparable devices.

Keywords: neurogastroenterology, enteric nervous system, paracrine signaling, Ileus, emesis, power propulsion, postprandial motility, interdigestive motility, gut defense, neural program library.

Introduction

The digestive tract is innervated by the autonomic nervous system and by sensory nerves that project from the gut to the brain stem and spinal cord. Three divisions of the autonomic nervous system innervate the digestive tract. Sympathetic, parasympathetic and enteric divisions make-up the autonomic innervation of the gut.

The enteric division, enteric nervous system (ENS), functions as an involuntary "brain-in-the-gut" that integrates gastrointestinal motility, secretion and blood flow into homeostatic patterns of gut behavior**.** Early electrophysiological evidence led to designating the ENS as a brain-in-the-gut for the first time in 1981 (Wood 1981). The heuristic model for the ENS is the same as for all independent integrative nervous systems, whether in brains and spinal cords of vertebrates or in invertebrates, such as the highly developed brain of the octopus (Sumbre et al. 2001). The octopus brain communicates with an independent neuronal plexus in each tentacle that is analogous to the ENS and provides integrative control for targeted movements of the tentacles in the capture of prey (Sumbre et al. 2001). The ENS, like the little brains in octopus tentacles, is an independent nervous system that coordinates and organizes the behavior of the musculature, secretory glands and vascular system, in each of the specialized organs of the gastrointestinal tract, into functional adaptive behavior in the series spacing of organs from esophagus to large intestine.

On the advice of his major professorial mentor, C. Ladd Prosser, the author began electrophysiological recording from neurons in feline ENS in 1967, with first results published in 1969 and 1970 (Wood 1970; Wood 1973; Wood 2016). Simultaneously, in the 1970s, electrophysiological studies of neurons in the ENS were done at the Pavlov Institute of Physiology of the Russian Academy of Sciences in St. Petersburg, Russia (Nozdrachev 1977; Nozdrachev et al. 1975a; Nozdrachev et al. 1977; Nozdrachev, Vataev 1981; Gnetov, Kachalov 1975a; Gnetov, Kachalov 1975b). The researchers at the Pavlov Institute were the first to record from neurons in the myenteric division of the ENS in situ with blood flow intact (Nozdrachev et al. 1975b; Gnetov, Kachalov 1975a; Gnetov, Kachalov 1975b).

Hierarchal neurophysiological organization

We now understand in 2019 that in the ENS, like most integrative nervous systems, the components are organized in hierarchal physiological order. Like most central nervous systems, neurophysiology of the ENS is organized in hierarchical steps from lower to higher levels of physiological complexity (Wood 1989; Wood 2012; Wood 2018). Axonal projections out of the hierarchical order to gastrointestinal effector systems determine minute-to-minute behavior of the muscularis externa, mucosal secretory glands and blood vasculature in the behaving gut. Integrated behavior of the musculature and secretory glands takes place as specific patterns of motility and glandular secretion that distinguish differing forms of behavior at levels of the esophagus, stomach, intestinal tract and gallbladder. Behavioral states, emphasized in this overview, reflect output from the uppermost levels of complexity. Recognizable behavioral states include: 1) Physiological Ileus; 2) Postprandial State; 3) Interdigestive State; 4) Defense; 5) Emesis; 6) Haustration.

Absence of contractile activity in the muscularis externa of the small and large intestine characterizes the behavioral state of physiological ileus. The postprandial behavioral state is especially obvious in the small bowel. It involves digestive behavior after ingestion of a meal and consists of segmenting (mixing) motility integrated with control of luminal pH and osmolarity at set-point values. The postprandial state reverts to the interdigestive state when digestion and absorption are completed. Motility in the interdigestive state is characterized by the migrating motor complex, which, in addition to specialized propulsive motility, initiates contraction of the gall bladder and secretion of bile into the duodenum (Wood 2012).

The bowel, when in the defensive behavioral state, is characterized by neurogenic hypersecretion and ortho- or retrograde power propulsion working in concert to expel quickly any agents in the lumen that threatens bodily integrity. Power propulsion in the upper small intestine is retrograde and reflects output of the emetic behavioral program in the ENS library. Power propulsion in the large intestine is mostly orthograde and associated with defecation.

The ENS library of programs in the large intestine has four neurogenically programmed patterns of behaviors recognized as: 1) haustral formation, 2) physiological ileus, 3) defecatory power propulsion; 4) defense.

Cellular physiology of neurons, glia and synaptic transfer of chemically coded information from neuron to neuron in integrated microcircuitry is in the lower and middle levels of the ENS neurophysiological hierarchy. Stored at the highest levels of organization of the hierarchy are programs for behaviors that emerge from the organization of the different kinds of neurons, their synaptic connections and their connectivity into circuits at lower levels.

A library containing a neural program for each of the digestive behavioral states mentioned earlier is stored at upper-most levels of complexity of ENS hierarchal organization. The function of each program in the library reminds one of the 21st century digitally programmed "apps" in the Apple® Inc. app store for smart phones, tablet computers and comparable devices. Accordingly, the ENS programs for the variety of independent behavioral states, found in the small and large intestine, are called "apps" in this overview. The author takes this liberty in recognition of an intellectually sharp medical stcudent, who suggested the analogy to him during a lecture. The student's "apps", of course, is a frivolous expression that will be used here to emphasize the analogy with computational neural programs in the highest levels of the hierarchy of neurophysiological organization in the ENS.

C. L. Prosser, Professor of Physiology at the University of Illinois, Champaign- Urbana campus, in the United States, taught students, in his comparative neurophysiology lectures, that acquisition of complete description of functions at lower levels of hierarchical organization in a nervous system does not predict behavior that emerges from a nervous system when it is responding and adapting to changes in its environment (Wood 2016). Nevertheless, knowledge of electrophysiological properties of single neurons and the synaptic connections of individual neurons inside configurations of neural circuits and networks at lower levels of a neurophysiological hierarchy is essential for understanding the physiology of independent integrative nervous systems like the ENS. For thorough understanding of normal and abnormal gastrointestinal physiology, awareness of how the components of the ENS work at each of the levels of hierarchical organization is essential.

Postprandial app

The postprandial app, in the small bowel of mammals, is triggered by the intake of a meal. This app programs the mixing (segmentation) pattern of motor behavior. Repetitive propulsive contractions of the circular muscle coat of the muscularis externa, which propagate over very short distances, account for the segmentation appearance when the app is "running". Circular muscle contractions in short propulsive segments are separated on either side by expanded receiving chambers with relaxed circular muscle and contracting longitudinal muscle, each of which reflect activity in short blocks of a hardwired polysynaptic propulsive circuit in a lower level of neurophysiological hierarchy (Wood 2012a; Wood 2018). The mixing motility

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continues at closely spaced sites along much of the length of the small intestine for such time as nutrients are present and sensed in the lumen.

Interdigestive app

The interdigestive app programs the migrating motor complex (MMC), which is the small intestinal motility pattern of the interdigestive state when digestion and absorption have been completed and nutrients are not present in the lumen (Wood 2012a; Wood 2018). The MMC starts as large amplitude contractions occurring at 3 per minute in human distal stomach. Activity starts in the antrum and continues to migrate into the duodenum and on through the jejunum 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 lower boundary (Wood 2012a; Wood 2018). The activity front slowly advances (migrates) down the intestine at a rate that progressively slows as it approaches the ileum. The circular muscle contractions in the activity front are reflections of the formation of the propulsive segment of a hard-wired propulsive motor circuit. Each propulsive wave traveling downward in the activity front consists of reflexively wired propulsive and receiving segment (Wood 2012a; Wood 2018). 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 a short distance beyond the boundary where the earlier one stopped. As a result, the entire activity front appears, on motility recordings, to migrate slowly down the intestine, "sweeping" the lumen clean as it travels. In 1969 discovery of the functions of this app by Joseph H. Suzurszewski inspired his mentor, Charles F. Code, to name the MMC "the bowel's housekeeper" because it slowly sweeps biliary secretions, sloughed epithelial cells and other nonessential contents downward and into the colon (Szurszewski 1969; Code, Marlett 1975; Code 1979). The physiological ileus app functions to keep the muscularis externa in "silent" mode along the bowel oral and aboral to the upper and lower boundaries of the migrating activity front. Neither MMCs nor physiological ileus can be found in the small intestine in the absence of a functional ENS.

Power propulsion app

The power propulsion app programs intestinal motility for rapid clearance of luminal contents from long segments of bowel during running of apps for specific behaviors, such as emetic motility in the small bowel and defense in the large intestine (Wood 2012a; Wood 2018). Power propulsive motility is characterized by strong, long-lasting contractions of the circular muscle coat of the muscularis externa that propagate over long distances in the small and large intestine. The contractions reflect formation of a specialized propulsive segment by of hardwired polysynaptic circuit and may be called "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 or in the mixing motility programmed by the postprandial app.

Giant migrating contractions have prolonged durations lasting for 18 to 20 seconds, when recorded in dogs (Otterson, Sarna 1994). They are the circular muscle contractile component in a propulsive segment formed by a hardwired circuit in the power propulsion app and underlie efficient propulsive motility that strips the lumen clean as they travel at about 1 cm per sec over long lengths of intestine in dogs. Motility programmed by the power propulsion app 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 independently 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 ileum and colon in the anal direction. Noxious mucosal stimulation is a trigger for calling-up this app and closing any other motility app that might be running. Cramping pain, fecal urgency and diarrhea are often associated with this motor behavior. Mucosal exposure to chemical irritants, introduction of luminal parasites, enterotoxins from pathogenic bacteria, allergic reactions and exposure to ionizing radiation are triggers for calling-up the aboral power propulsion app. Physiological features of this nature suggest that this app is a protective adaptation for rapid clearance of threats from the intestinal lumen.

Defensive app

The defensive app safeguards and protects bodily integrity. Defensive Immuno- neural plasticity of this nature at high levels of ENS neurophysiological organization is apparent in infections with intestinal parasites, such as *Trichinella spiralis*. Repetitive propulsive complexes occur that are significantly stronger than in uninfected controls in terms of volumes of luminal liquid moved by each complex as it occurs in segments of guinea pig jejunum *in vitro* (Alizadeh et al. 1987). The motor effects of first time *T. spiralis* infections subside within ten to twenty days of infection. Reinfection triggers the same motility response. However, due to integration of immune memory and ENS control, the behavioral response persists for extended periods of two or more months (Alizadeh et al. 1989).

Aborally directed power propulsion is a behavioral component of a more highly organized defensive app centered in higher levels of the ENS organizational hierarchy. The defensive app is called-up by paracrine exposure to neuromodulators released during degranulation of enteric mast cells (Wood 2012b; Wang et al. 2013; Wang et al. 2014). Reconfiguration of the synaptic networks by an overlay of mast cell degranulation products integrates output of a secretomotor app with output of the power propulsion app in a timed sequence (Wood 2012b; Wang et al. 2013; Wang et al. 2014).

The secretomotor app runs first and evokes voluminous mucosal secretion of electrolytes and H_2O that "flushes" threats, which might consist of infectious microorganisms, allergins or noxious substances, into the lumen and holds them in suspension. The neurogenic secretomotor response is followed immediately by running of power propulsion in the anal direction. Power propulsion rapidly propels the large volume of liquid toward the anus. Arrival in the recto-sigmoid region causes rapid distension, which triggers the recto-anal reflex and relaxation of the smooth muscle of the internal anal sphincter. Opening of the internal anal sphincter, in this situation in humans, underlies sensations of fecal urgency and emotional anxiety because the only remaining protection against incontinence is spinally evoked contraction of the skeletal muscle of the puborectalis and external anal sphincter (Wald 2018). Cramping abdominal pain reflects the excessive force of the propulsive contractions evoked during power propulsion. Symptoms of acute explosive watery diarrhea occur at this point in running of the app.

Neurophysiology of the defense app in mammals is reminiscent of polymorphic neural network described in the stomatogastric ganglion of lobsters where a defined neural network is reconfigured in different ways to form different functional outputs to the same effector system or systems, as evidently occurs in intestinal tract of vertebrates (Bucher et al. 2006). Reconfiguration of the output from the lobster network is accomplished through the selective release of dopamine and serotonin as neuromodulatory substances that overlay the entire network in paracrine manner and act to alter the electrical and synaptic behavior of the neural elements in the microcircuits of the network. Paracrine overlay of mast cell degranulation signals starts the defense app in the same manner in the ENS (Bucher et al. 2006).

Emetic app

The emetic app programs the specialized motor behavior in the small intestine during emesis. During emesis, the direction of power propulsion in the upper one-third of the small intestine is reversed for rapid transport of the luminal contents toward the stomach (Lang 2016). Controlled opening of the gastric pylorus by the ENS permits entry into the stomach and filling of the gastric reservoir. Retching, which is under control of the central nervous system as well as the ENS, empties the reservoir. The ENS then opens the lower esophageal sphincter and retching empties the stomach of vomit.

Emetic behavior is called-up from the library of apps either by commands from the brain or by local sensory detection of threatening substances in the lumen (Lang 2016). Like the power propulsion app in the distal small and large intestine, the adaptive significance of the emesis app is rapid removal of undesirable contents from the lumen of the upper bowel.

Physiological ileus app

Physiological ileus is adapted here as a term to describe absence of motility and propulsion in the small and large intestine which is not pathological. It is a basic behavioral state of the intestinal tract where an ENS app programs quiescence of motor function. Physiological ileus disappears after destruction or blockade of the ENS. Disorganized and non-propulsive contractile behavior occurs continuously due the autogenic contractile properties of unitary type intestinal smooth muscle when ENS functions are anesthetized or destroyed by pathological processes (Wood 1972; Brann, Wood 1976).

Quiescence of the intestinal muscularis externa reflects the operation of an app in which synaptic connections in ENS propulsive motility circuits are closed. ENS inhibitory musculomotor neurons evoke this behavioral state by firing continuously and suppressing responsiveness of the muscularis externa to electrical slow waves entering from interstitial cells of Cajal. Physiological ileus is a normal behavioral state in effect for varying periods of time in different intestinal regions depending on circumstances, such as the time after a meal. When the interdigestive motor app (MMC) is running, the small intestine persists in a state of physiological

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ileus in the regions of intestine on either side of the migrating activity front (Wood 2012a).

Medical literature describes "ileus" as being mechanical, "dynamic" or "adynamic" obstruction of the bowel. Adynamic ileus (paralytic ileus) is pathological obstruction of the bowel due to a paralytic-like state of the muscularis externa. Dynamic ileus, on the other hand, is pathological intestinal obstruction due to spastic contraction (i. e., failure to relax) of the circular muscularis externa in a segment of bowel. In view of the defined characteristics of pathological ileus, "physiological ileus" was invented as a useful term for referencing the non-pathological absence of motility in the small and large intestine. It is a normal state of the bowel in which the ENS programs quiescence of motor function through its control of inhibitory innervation of the smooth musculature.

The physiological ileus app runs for varying periods of time in different intestinal regions depending on extrinsic factors, such as the time after a meal and inhibitory noradrenergic input from sympathetic postganglionic neurons during physical exercise.

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