

Effects of the Autonomic Nervous System, Central Nervous System and Enteric Nervous System on Gastrointestinal Motility**P. M. K. REDDY***Department of Pharmacy, Mbarara University of science and Technology (M. U. S. T) P. O Box 1410 Mbarara Uganda.*

The gastrointestinal tract is chiefly involved in the digestion of ingested food, facilitation of absorption process and expulsion of the undigested food material through motility process. Motility is influenced by neurohormonal system which is associated with the enteric nervous system, autonomic nervous system and the higher centres in the brain. Many GIT diseases are characterized by altered function of the neurohormonal system associated with it, leading to various functional disorders. Characterization of various physiological factors involved in motility may lead to the development of specific drugs which may either enhance or decrease motility in various pathological conditions. A number of clinically used drugs including metoclopramide, cisapride and domperidone alter gastrointestinal motility via the modification of neurohormonal system. Targets need to be identified in several places in the enteric nervous system to normalize the deranged activity of gastrointestinal tract. The ultimate goal in managing patients with gastrointestinal disorders is to relieve symptoms and thereby improve the quality of life. In this review article, an exhaustive literature search was carried out to reveal the potential of important physiological systems that regulate gastrointestinal motility.

Keywords: *Enteric nervous system, Intestine, gut, autonomic nervous system*

INTRODUCTION

The gastrointestinal tract starts with posterior pharynx to the anus. It is chiefly associated with digestive and absorptive functions which depend on a variety of mechanisms that soften the food, mix it with hepatic bile and digestive enzymes secreted by various glands such as salivary glands and the pancreas to facilitate digestive process, to transport the digested products across the mucosa and to expel undigested products through the distal portion [1]. To integrate the motility / motor activity of the gut, a complex neurohormonal regulatory system controls contraction and relaxation of the different muscle layers and sphincters. This neurohormonal control takes place at three levels namely the enteric nervous system, autonomic nervous system and

higher centres of the central nervous system [2].

Enteric Nervous System

The enteric nervous system (ENS) is a large and highly organized collection of neurons located in the walls of the GIT. It is sometimes considered as third division of the autonomic nervous system [3]. The neuronal network of ENS receives preganglionic fibres from the parasympathetic system and postganglionic sympathetic axons. Fibres from the cell bodies in the network of ENS travel to the smooth muscle of the gut to control motility and to secretory cells in the mucosa [3]. Many digestive diseases are characterized by altered structure and / or function of the ENS, including inflammatory, infectious, and degenerative and the so-called

functional disorders, in which no structural or biochemical abnormalities are clearly identifiable. Nevertheless, life-threatening, functional disorders have acquired importance as a growing field in medicine because of their increased incidence, tremendous impact on patient's quality of life, and high economic and social costs [4]. Visceral perception, intestinal motility and secretion are regulated by a considerable number of transmitters and receptors in the ENS. About five targets have been identified in several places in the ENS, from the points of transduction of sensory information to the neuroeffector junctions [4, 5]. These are smooth muscle cells (for motility), mucosal secretory cells, gastrointestinal endocrine cells, gastrointestinal microvasculature which maintains mucosal blood flow during intestinal secretion and immunomodulatory and inflammatory cells that are involved in mucosal immunologic responses.

Autonomic Nervous System

Autonomic nervous system (ANS) acts as a junction between ENS and central nervous system. The connections that form this union, with respect to the intestine, follow the two routes of nerves in the ANS, the craniosacral and thoracolumbar pathways. The craniosacral pathways involve both cranial (vagal) and sacral (pelvic) segments, that end in nerve cells, are cholinergic in nature and their effects are called parasympathetic or those that cause increase in motility of GIT. Whereas thoracolumbar motor pathways terminate in a nerve cell within prevertebral ganglia that is adrenergic in nature and their effects are called sympathetic or those that cause decrease in motility of GIT. The ANS performs important reflex and possibly rhythm clock functions as well [2].

Central Nervous System

The higher centres of the central nervous system (CNS) in the brain constitute the third level of control of gut motility. Central nervous system controls certain integrative

functions such as antrointestinal coordination. Under special circumstances such as during stress, the CNS can override the autonomy of the gut and modify its pattern of activity. These effects have been demonstrated experimentally in humans with labyrinthine stimulation or cold stress during the fed state. A similar situation may be observed during nausea and vomiting, in which some of the motor patterns that appear in the gut are induced by the CNS via the vagi [2].

CNS – ENS Circuits. The ENS is well connected to the CNS through both motor and sensory pathways of the sympathetic and parasympathetic nervous system of ANS. Parasympathetic activity generally increases the activity of intestinal smooth muscle and sympathetic activity decreases but causes sphincters to contract [1].

Parasympathetic Nervous System (PNS): The PNS is considered to be the major system controlling motility of intestine. Its preganglionic fibres consist of about 2000 vagal efferents and other efferents in the sacral nerves. They generally end on cholinergic nerve cells of the myenteric and submucous plexuses [1]. The motor pathways consists of the vagus nerves that control upper GIT and the sacral nerves that regulate the distal colon and rectum. However, in small bowel vagal preganglionic neurons innervate only small clusters of selected myenteric neurons. These differences in the intensity of innervation by parasympathetic fibers reflect the fact that the CNS exerts direct control of the oesophagus, stomach and rectosigmoid parts of GIT and less direct control on the small intestine and proximal colon [5]. The preganglionic neurons are all cholinergic and exert excitatory effects on enteric neurons through nicotinic and in some regions, muscarinic receptors. The PNS contracts the smooth muscle by releasing the neurotransmitters acetylcholine (ACh) and ATP and relaxing sphincters by releasing nitric oxide [6]. These circuits indicate that

the ENS and CNS are closely linked and have profound influences on each other.

Sympathetic Nervous System (SNS): The SNS nerve fibers entering the gut consist of adrenergic, postganglionic fibers with cell bodies in the prevertebral ganglia (nodose ganglia), comprising of coeliac, superior and inferior mesenteric ganglia. But, many of them end on postganglionic cholinergic neurons, where the norepinephrine they secrete inhibits ACh secretion by activating α_2 -presynaptic receptors. Other sympathetic fibres end directly on intestinal smooth muscle [1]. Their input regulates intestinal motility, blood flow, water and electrolyte secretion [7]. The Falck-Hillarp technique revealed that sympathetic innervation was very scarce to the major part of smooth muscle layers, and most of the adrenergic fibers contact with one of the two major plexuses. However, the sympathetic innervation is seen in the mucosa in particular around the crypt epithelium [8]. There is an experimental evidence for adrenergic inhibition of local excitatory motor reflexes and /or extrinsic excitatory parasympathetic nervous activity [9].

Net work of enteric nervous system

Studies about extrinsically denervated intestine by Bayliss and Starling (1899), Langley and Magnus (1905) and Trendelenburg (1917) revealed that isolated intestine possess its own nervous system to coordinate inherent contractions or peristaltic reflex [10-12]. It is probably because of this self-contained neural apparatus that the ENS still functions after surgical interruption of the extrinsic innervation of the gut through vagotomy or sympathectomy and or spinal cord injury. The ENS may actually be the 'talk back' to ganglia relaying input from the CNS. The independence of the ENS was not only established but actually recognized long ago. Langley (1921) in his classical description classified the ENS as a third division of the ANS [13]. In humans, there are about 2×10^3 efferent fibers in the abdominal vagus

nerves, while there are more than 10^8 ganglion cells in the intestine, a number that is of the same order of magnitude as the number of neurons in the human spinal cord [14, 15]. The ENS is primarily derived from cells of the vagal segment of the neural crest that migrate to the cranial portion of the gut and subsequently move caudally to populate the entire GIT [17].

The array of ganglia occurs in two layers. The myenteric plexus (plexus of Auerbach's) occupies the intermuscular space between circular and longitudinal layers and provides motor innervation to the two muscle layers and secretomotor innervation to the mucosa [5]. The other one as submucous plexus (Meissner's) lies within the submucosa between the circular muscle and muscularis mucosa and innervates the glandular epithelium, intestinal endocrine cells and submucosal blood vessels and is primarily involved in the control of intestinal secretions. Process from these ganglion cells form dense networks in these two planes and also extend to interconnect the two main plexuses and to innervate the three muscle layers. The neurotransmitters in the system include ACh, the amines norepinephrine and serotonin, the amino acid gamma amino butyric acid (GABA), the purine ATP, the gases nitric oxide (NO) and carbon monoxide (CO) and many different peptides and polypeptides [1]. A key property of the ENS is its ability to program relatively complex tasks, such as the peristaltic reflex that enables progression of the dietary bolus [2].

Extensive studies over last 20 years lead to identification of all major neuronal types in small intestine of guinea pig thus making the guinea pig a model of the organization of ENS circuits. Kunze and Furness (1999) depicted circuit of neurons being in series, where numerous connections between neurons mean that they act as assemblies with both in-parallel and in series connections [20]. There are 2,500 nerve cells/mm length of gut guinea pig' intestine

and 1 mm containing the cell bodies of 400 inhibitory motor neurons and 300 are of excitatory motor neurons as well as the cell bodies of about 120 ascending and 120 ChAT (Choline Acetyl Transferase) /NOS (Nitric Oxide Synthase) descending interneurons. A large proportion of the remaining neurons are longitudinal muscle motor neurons which account for 500 nerve cell bodies/mm. There are also small population of ChAT/Somatostatin (4%), ChAT/5-HT (2%) and ChAT/VIP (3%) which are descending interneurons [20]. Dogiel (1899) identified different morphological types of enteric neurons [21]. Dogiel type I neurons possess a single axon and short lamellar dendrites which Dogiel type II cells have multiple long processes.

Motor Neurons: Motor neurons are responsible for contraction and relaxation of intestine. Both stomach and intestine are dually innervated by excitatory and inhibitory motor neurons whose cell bodies are in the gut wall. In the stomach these can be activated by stimulation of vagus. Acetylcholine was found to be the primary neurotransmitter in excitatory motor neurons [7, 20]. However, Grider (1989) showed that pharmacological blockade of cholinergic transmission to the muscle does not completely abolish excitatory transmission, still a residual transmission is visible which is abolished by antagonism of tachykinin receptors [22]. These two components of transmission form a single neuron type which is demonstrated by immunoreactivity for both ACh and tachykinins which are synthesized by ChAT. They are divided into excitatory circular muscle motor neurons, inhibitory circular muscle motor neurons and longitudinal muscle motor neurons.

Interneurons: This is to indicate the existence of neurons with cell bodies in the myenteric ganglia and terminals in ganglia lying anal or oral. There is an input to the chains of interneurons that run orally and anally and at each point there is output from the chains to motor neurons then to the muscle [20]. Lepard *et al* (1997) reported

that ATP is a putative neurotransmitter at fast excitatory synaptic transmission between the descending interneurons or between interneurons and inhibitory motor neurons [24].

Ascending interneurons: They are most important class of enteric neurons (Dogiel type I), albeit being few [25]. They project orally within the myenteric plexus to synapse with the final excitatory circular muscle motor neurons via fast nicotinic and non-cholinergic slow synaptic outputs [25]. They receive fast synaptic inputs from other ascending interneurons and from primary afferent neurons. They contain enzymes for ACh, tachykinins and opioid peptides.

Descending interneurons: Five types were identified in guinea pig intestine. They project aborally to synapse with other myenteric neurons [26]. In contrast, descending reflexes are resistant to the nicotinic antagonist, hexamethonium [27].

Intrinsic Primary Afferent Neurons (IPAN). These are the first neurons in the intrinsic nerve circuits activated by luminal stimuli. They are morphologically Dogiel type-II neurons, were shown to be excited by mucosal sensory stimuli including acid, short-chain neutralized fatty acids and 5-HT or radial stretch. 5-hydroxytryptamine is an essential transmitter in reflexes initiated from mucosa [20]. There are total about 650 IPANS / mm of intestine present in both myenteric and submucosal plexus. They represent about 30% of myenteric neurons and 14 % of submucosal neurons, project to the villi and circumferentially to synapse with myenteric ascending interneurons, descending interneurons, longitudinal muscle motor neurons, excitatory circular muscle motor neurons, and inhibit circular muscle motor neurons [28].

Opioid neurons. Opioid neurons constitute the largest population of peptide-containing neurons in the myenteric plexus of the gut. They contain either Met-enkephalin or Leu-enkephalin. Their neurons are Dogiel Type

I/S which possess several dendritic processes extending orad within the plexus and one long axonal process extending into the underlying circular layer [20, 29].

Excitatory nerves. Most excitatory nerves that increase contraction force are cholinergic. Acetylcholine is the responsible neurohormone, but not the sole excitatory neurohormone substance which is evident from studies conducted *in vitro* and *in vivo* [20].

Inhibitory nerves. Most inhibitory nerves that depress contraction force, release a transmitter that is not yet identified. It was once proposed and widely accepted that norepinephrine is responsible, but this was later discredited [20]. Consequently, the inhibitory nerves to the intestinal muscle are referred to as the non-adrenergic –non-cholinergic (NANC) nerves. Various candidate substances for this unknown inhibitory transmitter are now under study including most prominently, vasoactive intestinal polypeptide (VIP), ATP, NO or other nitrogenous compounds [5].

Other muscle excitation mechanisms

The intestinal smooth muscle cells have stretch-activated channels whereby stretch of muscle causes their excitation [30]. The smooth muscle cells are electrically coupled through gap junctions. It is thus possible to control an entire layer of smooth muscle by releasing the transmitter only at the myenteric plexus-smooth muscle interface [16].

Electrical and Mechanical activity:

Except in the oesophagus and the proximal portion of the stomach, the smooth muscle of the GIT has spontaneous rhythmic fluctuations in membrane potential between -65 and -45 mV. This basic electrical rhythm (BER) is initiated by the interstitial cells of Cajal (ICC), stellate mesenchymal pacemaker cells with smooth muscle-like

features that send long multiply branched processes into the intestinal smooth muscle. In the stomach and small intestine, these cells are located in the outer circular muscle layer near the myenteric plexus while in the colon they are at the submucosal border of the circular muscle layer [1].

The visceral smooth muscle is characterized by the instability of its membrane potential and by the fact that it shows continuous irregular contractions that are independent of its nerve supply. This maintained state of partial contractions is called tonus or tone. Thus the excitation contraction coupling in visceral smooth muscle is a very slow process compared with that in skeletal / cardiac muscle. Calcium is involved in the initiation of contraction of smooth muscles. However visceral smooth muscles generally has a poorly developed sarcoplasmic reticulum and the increase in intracellular calcium concentration initiates contraction due to Ca^{2+} influx from the extracellular fluid via voltage gated Ca^{2+} channel.

Visceral smooth muscle is unique from other types of muscle because it contracts when stretched, in the absence of any extrinsic innervation [20]. Stretch causes a decline in membrane potential, an increase in the frequency of spikes and a general increase in tone. If adrenaline or nor-adrenaline added to an intestinal smooth muscle preparation, the membrane potential becomes larger, the spikes decrease in frequency and muscle relaxes. When ACh is added *in vitro*, the membrane potential decreases and spikes become more frequent, the muscle become more active with an increase in tonic tension and the number of rhythmic contractions. This effect is mediated by phospholipase C_4 , IP_3 , through increase in the intracellular Ca^{2+} concentration [20].

Peristalsis

Peristalsis is a reflex response that is initiated when the gut wall is stretched by the contents of the lumen. It occurs in all parts of the GIT from the oesophagus to the rectum. The wave of contraction then moves

in an oral-to-caudal direction, propelling the contents of the lumen forward at rates that vary from 2 to 25 cm/s. Peristaltic activity can be increased or decreased by the autonomic inputs to the gut, but its occurrence is independent of the extrinsic innervation. Peristalsis is a good example of the integrated activity of the ENS [1]. It involves the release of 5-HT by mucosal stimulation or mechanical distention of the gut lumen which triggers activity in the intrinsic afferent neurons. Above the site of the stimulus, ascending cholinergic interneurons relay the signal to excitatory motor neurons containing ACh and substance P. As a result the circular muscle layer above the stimulus contracts. At the same time, below the stimulus site, descending cholinergic interneurons activate inhibitory motor neurons that contain NO, VIP and ATP thus causing relaxation. The resultant forces propel the bolus in an antegrade direction. As the bolus moves, it triggers similar local peristaltic reflexes at successive sites along the gut [5].

Migrating motor complex

During fasting between periods of digestion, the pattern of electrical and motor activity in GIT smooth muscle becomes modified so that cycles of motor activity migrate from the stomach to the distal ileum. Each cycle or migrating motor complex (MMC), starts with the quiescent period (phase I), continues with a period of irregular electrical and mechanical activity (phase II) and ends with a burst of regular activity (phase III). The MMCs migrate aborally at a rate of about 5 cm/min and they occur at intervals of approximately 90 min [1]. Their function is unsettled, although gastric secretion, bile flow and pancreatic secretion increase during each MMC. They may clear the stomach and small intestine of luminal contents in preparation for the next meal. MMC activity is stopped by ingestion of food, with a concomitant return of peristalsis [1].

CONCLUSION

ANS reciprocates actions between CNS and ENS. It can increase or decrease motility by stimulation of its parasympathetic and sympathetic branches and also cause sphincters to contract. Hypermotility due to excitation of parasympathetic system can be controlled by atropine or metoclopramide. The CNS chiefly coordinates the antrointestinal motility through its motor and sensory pathways. The CNS exerts direct control of the oesophagus, stomach and rectosigmoid parts of GIT. Its effects are perceived during stress causing hypermotility leading to diarrhea and vomiting in motion sickness. These affects can be controlled by drugs acting on brain such as loperamide and scopolamine bromide. The ENS is central to normal gut function and is involved in most disorders of GIT. It has ability to program relatively complex tasks, such as the peristaltic reflex that causes progression of the dietary bolus. Even when the primary pathology lies in another part of the gut, the ENS still serves as the effector neural controller, leading to a disturbances in gut function and generation of symptoms. Therefore, ENS serves as a useful therapeutic target for disorders of GIT such as distal ulcerative colitis which is managed using enemas containing lignocaine. Opioid analogues act on enteric neurons to diminish large bowel motor and secretory function. Moreover, a number of clinically used drugs that alter gastrointestinal motility act via the ENS.

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