UNIVERSAL WISER
PUBLISHER

Enteric and Central Nervous System Mediated Control of Digestive Processes in the Small Intestine: a Coprocessor-Processor Paradigm

Ravi Kant Avvari
Sasi Institute of Technology and Engineering, Tadepalligudem, West Godavari, Andhra Pradesh, India - 534101
E-mail: ravikant.iitk@gmail.com

Abstract: The small intestine is part of the gastrointestinal tract that facilitates further breakdown of the meal, extract the nutrients, absorb them efficiently and expel the left over remains of the digesta. They help in managing various digestive processes that involve buffering of the chyme, mixing with small intestinal secretions and bile, absorption and transport. In general, the small intestine functions as a bioreactor in an efficient way by employing neurohormonal means for regulating the digestive processes. Part of the regulatory functions involving-eliciting motility patterns, control of secretions and emptying of the bowels are locally mediated by the enteric reflexes, however the physiological functions demanding homeostasis requires the intervention of the central nervous system. In this review, we explore the nature of regulating mechanisms that are managed partly by the enteric nervous system (ENS) as analogous to a coprocessor and works in conjunction with the central nervous system (CNS), the primary processor to manage the extensive task of digesting the meal.

***Keywords*:** digestion, small intestine, small intestinal motility, local longitudinal shortening, central nervous system (CNS), enteric nervous system (ENS), enteric reflexes, vago-vagal reflex

1. Introduction

The small intestine is the part of the digestive system that receives partially digested meal from the stomach via a pyloric sphincter and empties the left over meal into the large intestine for further processing. The luminal contents of the small intestine or the digesta, that has already been grounded and blended with the digestive enzymes under acidic conditions in the stomach, is now in the granular form. Further digestion is performed under alkaline condition where the digestive enzymes of the intestine and pancreas, together with the biliary secretions (emulsification of fat) help facilitate the digestion at the molecular level. Much of the digestion occurs in the long convoluted tube of the small intestine that spans nearly 7 meters in length with nearly uniform cross-section of 2.5 cm diameter. They also act as a mediator for collecting nutrients from the meal. The nutrients then enter into hepatic-portal circulation (esp. the superior mesenteric vein) to the liver, wherefrom they enter into systemic circulation. The rich supply of blood ensures that these nutrients are transferred to the cells to perform their physiological function.

2. Role of mechanics in digestion

The small intestine comprises of the uppermost part known as the duodenum (~25cm in length), followed by the adjacent segments known as the jejunum and the ileum. These segments play their role in digestion that is remarkably different from each other. Studies relevant to the mechanophysiology of the small intestinal segments are rare. It can, however, be generalized that the small intestinal segment participates in digestion by eliciting smooth muscle contractions (small intestinal motility) which leads to generation of mechanical forces, local to the segment, sufficient enough to develop flows in the lumen [1]. The nature of flows developed in the lumen directly related to the nature of motility or motility patterns elicited by the small intestine. In other words, depending on the motility patterns elicited, the shearing of the luminal contents take place which are responsible to cause mixing and shearing of the contents [2]. Not all the contraction causes mixing, specific motility pattern also helps to propel the contents aborally so further processing can take place in the lower segments of the small intestine.

According to the *in silico* model of the antro-pyloro-duodenal (APD) segment, as proposed by the author [3], is a

DOI: https://doi.org/10.37256/fse.112020143

dynamic segment of the gut that coordinate with each other, preferably via enteric reflexes, to develop various kinds of the motility to perform their specific physiological function of mixing and transport. Clinical studies demonstrate the need for segmental contractions to facilitate the process of fat emulsification by the biliary secretions. Coordination of the muscular contractions of the antrum, pyloris and the duodenum is critical in regulating the flow across the pylorus (gastric emptying or duodenogastric reflux); otherwise may lead to excessive flow of toxic chemical of the biliary secretions into the stomach that is detrimental to mucosal barrier and gastric mucosa [1, 4]. Contractions of the duodenal muscles also serve the purpose of buffering the acidic chyme (gastric digesta), preferably through segmentation. The segmentation (motility patterns characterized by multiple numbers of waves contracting over the segment) helps to develop flow patterns to facilitate the process of mixing the contents and replenishing the fluid near the mucosa with fresh contents; thus increasing fluid contact with the walls of the small intestine. The numerous folds in the small intestine provide a multi-fold increase in its surface area so as to allow for efficient absorption of the nutrients. In addition to this, there also exist numerous folds on the epithelial cell known as microvilli (protrusions of the epithelial cell) that create tiny pockets and increase the contact between the cells and chyme. The folds in the small intestinal walls comprises of three types - folds of the mucosal wall (plicae), finger like projection (villi) and brush border on apex of the cells (microvilli). These three components altogether increase the net effective surface area of contact with the luminal contents by approximately 600 fold. Such extremely higher surface area of contact allows for increased rate of digestion and absorption at the surface, which otherwise may affect the rate of delivery of the energy rich nutrients to the body. Thus, suggesting that the entire structure of the small intestine is optimized for the purpose of absorption of nutrients. By the time the nutrient rich contents have passed through the long segment small intestine (esp. the jejunum), about 90% of all available nutrients have been absorbed into the body. The ileum is responsible for absorption of the vitamin B12, bile salts and the left over nutrients unabsorbed during the jejuna transit. The structured organized of the small intestine into duodenum, jejunum and ileum allows for differential treatment of the contents as they move along the segment. Whereas the duodenum helps in buffering the chyme (gastic content entering into the duodenum) and pre-processing the chyme for further digestion, the jejunum is responsible for maximal absorption. While ileum also absorbs the nutrients that are left over, their absorptive function is secondary and participates in post-processing of the meal and immune response (ileum has abundant Peyer's patches). The ileocecal junction interconnecting the small and large intestine acts as a sphincter and prevents reflux of large intestinal contents (rich in bacteria) into the small intestine [5].

3. Eliciting optimal motor patterns

Coordinated contractions of the smooth muscle fibers of the circular and longitudinal layers is necessary for optimal contractility (for optimal digestion) and optimizing the energy spend on developing small intestinal motility patterns for the purpose of digestion. Whereas the circular fibers contract to close the lumen, the longitudinal fibers shorten the segment axially to concentrate more circular fibers to help reduce the tensile force per unit length of the circular muscle fiber during rigorous contraction [6, 7]. Such mechanical advantage is utilized during the pumping of highly viscous fluid and dilatants (shear thickening fluid) during course of highly occlusive peristalsis [2].

Eliciting motor patterns in the small intestine are governed by the complex network of neurons which are referred to as the enteric circuit [8]. Depending on the state of the digestive system, the neuro-hormonal circuits (enteric nervous system and the central nervous system in coordination with the hormones) initiates the complex task of digestion by eliciting appropriate motor patterns.

Whether to initiate the digestive or the inter-digestive motility patterns is determined by the vagus. The interdigestive patterns, collectively known as the migrating myoelectric complex (MMC), comprises of various phases which repeats periodically every 80-110 min in humans [9, 10]. They essentially are the home-keepers of the gut which expels out any undigested matter left over after digestion. The borborymus sounds in abdomen are due to strong MMC contractions; noise arising from the movement of the gas-liquid mixture through the bowels. They occur in synonymous with peak hormonal concentration of motilin.

With ingestion of meal, the vago-vagal reflex switches the inter-digestive motility patterns (characterized by those having MMC phases-quiescent, regular and irregular phases) to fed state pattern. Studies involving vagal blockade (vagal cooling or vagotomy) were found to abolish the coordination in motility patterns between the antrum and the pylorus and abolishes the occurrence of spontaneous and ghrelin-induced gastric phase III-like contractions, suggesting that gastric phase III-like contractions are mediated by vagal cholinergic pathways [11, 12]. The shift in the nature of motility patterns to fed-state (regular contractions having frequency characteristics of the slow waves local to the segment) is an adaptation to process the meal that may be fluid-like or semi-solid. According to Takahashi [13, 14], the vago-vagal reflex mechanism

involves the following sequence of step-firstly, release of motilin (a gut hormone involved in motility control) from the duodenal mucosa, stimulation of the enterochromaffin cells (EC) to release 5-hydroxytryptamine (5-HT), followed by the activation of the 5-HT receptors of the vagal afferents, transfer of this information via neural transmission to nuclei center (nucleus tractus solitaries, NTS; and dorsal motor nucleus of vagus, DMV) of the brain stem, and finally leading to the generation of activation of the efferent neurons leading to smooth muscle contractions of the small intestinal muscles (muscularis externa). Such a feedback mechanism essentially helps in determining as to whether elicit the MMC phase III type motility pattern or not to elicit.

Motility patterns are fine tuned to the type of meal ingested; non-nutrient liquid meal show no prominent motility signatures, while meal containing fat triggers the enteric reflexes to suppress the pyloric sphincter so as to reduce the rate of inflow of nutrient rich meal into the duodenum. The reflex mechanisms are tightly regulated to ensure reliable digestion; otherwise may lead to problems of dumping syndrome (rapid gastric emptying) or gastroparesis (slow gastric emptying). Gastric emptying that is rate-limited by the intestinal capacity to process the meal (3 kcal/min) proceeds over duration of 1-2 hours after a meal; solid food shows latency time to gastric emptying by approximately ½ an hour, the time required to ground the meal. While the digestion involving both chemical and mechanical process occurs in unison throughout the small intestine, absorption of the nutrients is also simultaneous. The process is rather slowest, since the chemical kinetics of reactions and rate of absorption are slow. The average transit time for the bolus to pass the human small intestine is around 3-4 hours; varies with meal type.

The control dynamics of digestion is majorly driven by the motility patterns which in turn are controlled in part by ENS, CNS and the hormones. Control of the gut function is established through feedback regulation mediated by the sensors. There are approximately 20 types of enteric neurons [15-18] which function as a sensory neuron (intrinsic primary afferent neurons or IPANs), interneurons and motor neurons. IPANs play a key role in sensing the physiological state of the gut such as the tension in the wall and chemical nature of the luminal contents. Based on the nature of stimuli detected by IPANs, specific enteric reflex circuits are activated to elicit appropriate motility patterns. They do so by controlling the activity of the excitatory and the inhibitory neurons which controls the smooth muscle activity. While the excitatory neuron helps in contracting the smooth muscle, the inhibitory neuron on the other hand suppresses the smooth muscle contraction. These neurons use different neurotransmitters to ensure separation of the physiological functions. In general, the excitatory neurons uses acetylcholine and tachykinins and the inhibitory neurons uses nitric oxide, vasoactive intestinal peptide (VIP) and ATP as modes of neurotransmission. Generation of peristalsis requires activation of the peristalsis reflexes (medicated by local enteric reflexes), and generation of various motility patterns for mixing and propulsion. Similarly, coordination among the muscle layers (circular and longitudinal muscle layer) also play key role in peristaltic pumping [7]. The biomechanical studies show that such coordination help the muscle to contract in way to optimize the power requirement of peristalsis pumping of the luminal contents, esp. in causation of flow patterns for mixing or transport [2, 6, 19]. Although the reflexes involved in conferring such coordination remains unclear [20, 21], clinical studies also support the concept of muscular coordination [7] suggesting the existence of reflex mechanism. Besides the small intestinal muscles, the enteric reflexes also help regulate the secretion of the mucosal cells and vasodilation.

4. Coprocessor-processor paradigm

The enteric nervous system forms the intrinsic nervous system of the gastrointestinal tract which regulates various physiological processes of digestion. In terms of computer engineering, we may relate ENS to as the coprocessor of the computer (for example 8087, the math co-processor) that is destined to supplement the functions of the primary processor (8086 microprocessor) or CPU (analogous to CNS in gut) independently; without the involvement of the CPU (Figure 1.) [22]. Numerous parallels can be drawn about the enteric circuits with the architecture of a computer. We believe that the nervous system also shares their obligation of digestion between the ENS and CNS. The ENS manages the lower level control of digestion through entero-enteric reflexes.

Functions that are independently managed by the ENS are as follows:

1. collecting information about the meal composition and rheology of the contents [22-24]
2. regulating duodeno-biliary-pancreatic secretions (locally mediated) [25, 26]
3. controlling small intestinal motility thorough enteric reflexes [27, 28]
4. managing short and long reflexes: peristalsis reflex, gastrocolic reflex (such as the distention of the stomach causes evacuation of the colon), and the enterogastric reflex (such as the distention of the small intestine reduces the gastric motilty) [29].

Whereas the details relevant to the energy demands of the body are unknown to the ENS, the CNS shares this

obligation to ensure efficient supply to the cells by assessing the energy requirements of the body and manifesting through gut-brain axis (bidirectional link between the ENS and CNS). They employ two divisions of the autonomic nervous system, namely the sympathetic and parasympathetic which exercises their influence over the motility pattern in a counteractive manner to help regulate the physiological function of the body as a whole. The enteric nervous system communicates with the central nervous system through the parasympathetic (such as the vagus nerve) and sympathetic (such as the prevertebral ganglia) nervous systems [30]. They relay the details of the sensory and motor signals between the ENS & CNS through this channel of communication. Managing functions at the level of central nervous system are distributed among discrete cell bodies organized as dorsal vagal complex which is located in the dorsomedial hindbrain medulla [31]. It comprises of dorsal motor nucleus of the vagus (DMV; contains preganglionic nerves that supply smooth muscle of the esophagus and the rest of the gut), and nucleus tractus solitarius (NTS; receives the sensory input from the viscera, act as a major relay center).

The CNS in coordination with the ENS helps manage the digestive process during various circumstances by,

1. inducing cephalic phase upon antipatory responses of meal ingestion [32]
2. modulation of duodeno-biliary-pancreatic secretions [33]
3. changing the small intestinal motility patterns [34]
4. regulating the appetite [35]
5. mediating symptoms of nausea and vomiting [36]
6. controlling via emotional and cognitive centers of the brain

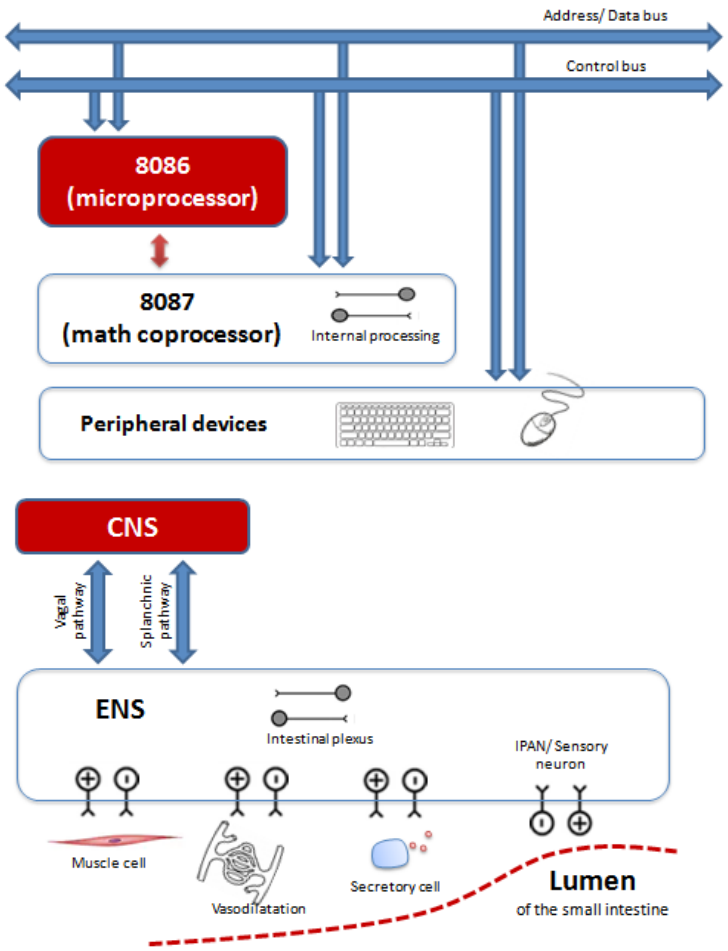

Figure 1. The processor – coprocessor paradigm model of the small intestine (bottom panel) compared to microcomputer system based on 8086 microprocessor (top panel). The 8086 microprocessor use control and data bus (group of interconnecting wires) for communicating with 8087 math coprocessor (supplements the functions of the processor by performing floating point arithmetic operations). As a counterpart, the communication is facilitated via neural pathways (vagal and splanchnic) in CNS-ENS system. The peripherals (externally connected devices such as mouse, keyboard and joystick) communicate to the 8086 microprocessor via control and data bus. While in contrast, the end effecters (such as muscle of the intestine and secretory cells of the mucosa) directly communicate to the ENS through nerve fibers (afferent and efferent). Note: Control of peripherals is directly mediated by the 8086 while in the small intestine the peripheral control is mediated by the ENS

Control of intestinal secretions has significance in digestion. Since mixing and transport form an integral part of the digestion, rheological nature of the digesta has to be tuned suitable for easy mixing and transit. The intestinal muscosa secretes mucous that allows for lubrication and protection from toxic chemicals and acid (such as in duodenum). Lubrication provides necessary slippage as a wave of contraction traverses the small intestinal segment; which otherwise may develop higher friction to resist the movement of digesta causing wearing of the mucosal layer. The slippage of the luminal contents helps in the development of the flow patterns for the purpose of mixing and transport. Easier the slippage, the fluid are subjected to wall momentum which helps in moving the fluid freely to cause the generation of circulating flows. Otherwise, the flows developed may not be efficient in mixing the contents. The motor neurons of the enteric nervous system manage the process of secretory control via submucosal plexus (part of the ENS). The process is governed by the enteric networks, where secretin (one of the gut hormone) released in response to acid in the duodenum, in synergy with activity of cholinergic and non-cholinergic enteric neurons helps to stimulate the pancreas and bile ducts to release their secretions (alkaline fluid) which in turn neutralizes the acid.

5. Conclusion

We conclude that small intestinal digestion is complex and involves participation of neuro-hormonal cues. The intelligence to digestion is mediated by the enteric and central nervous system that helps initiate various events for the preparation of digestion and the digestion. While preparation of digestion involves secretion of the digestive juice into the small intestinal lumen, digestion is initiated by the motion of fluids in the lumen that are developed by contractions of the smooth muscle fibers of the small intestine. Whether to digest to a lesser or greater extent is decided by the nature of food and the digestive demand. The small intestine employs a network of sensors (pH, protein, fat) to regulate the digestion via feedback. A coprocessor-processor paradigm model of the small intestine may provide insights into the pathophysiology of the system and in devising better therapeutics for managing patients with digestive disorders.

Conflict of interest

The author declares no competing financial interest.

References

[1] Avvari RK. Biomechanics of the Small Intestinal Contractions. In: Qi DX, editor. *Management of Digestive Disorders: Intech Open*. 2019.

[2] Avvari RK. Effect of local longitudinal shortening on the transport of luminal contents through small intestine. *Acta Mechanica Sinica*. 2019; 35(1).

[3] Avvari RK. *Bio-mechanics of the distal stomach and duodenum: An insight into mechanisms of duodenogastric reflux and duodenal mixing: 48th Graduating Students Convocation, Indian Institute of Technology Kanpur*. 2015.

[4] Sarna S.K, Kitai R, Muniappan K, et al. Gastroduodenal coordination: a computer analysis (Abstract). In: Duthie H.L. (eds) *Gastrointestinal Motility in Health and Disease*. Springer, Dordrecht: 1978.

[5] Essam Imseis, Fernando Navarro, Ursula Nawab, et al. Chapter 17-*Controversies in Short Bowel Syndrome, in Gastroenterology and Nutrition: Neonatology Questions and Controversies* (Second Edition). 2012; 237-250.

[6] Pal A, Brasseur JG. The mechanical advantage of local longitudinal shortening on peristaltic transport. *J Biomech Eng-T ASME*. 2002; 124(1): 94-100.

[7] Nicosia MA, Brasseur JG, Liu JB, et al. Local longitudinal muscle shortening of the human esophagus from high-frequency ultrasonography. *Am J Physiol Gastrointest Liver Physiol*. 2001; 281(4): G1022-33.

[8] Costa M, Brookes SJH, Hennig GW. Anatomy and physiology of the enteric nervous system. *Gut.* 2000; 47: 15-19.

[9] Takahashi T. Mechanism of Interdigestive Migrating Motor Complex. *J Neurogastroenterol Motil.* 2012; 18: 246-257.

[10] Deloose E1, Janssen P, Depoortere I, et al. The migrating motor complex: control mechanisms and its role in health and disease. *Nat Rev Gastroenterol Hepatol*. 2012; 9(5): 271-85.

[11] Hall KE, El-Sharkawy TY, Diamant NE. Vagal control of migrating motor complex in the dog. *The American journal of physiology*. 1982; 243(4): G276-84.

[12] Khan IH, Bedi BS. Effect of vagotomy and pyloroplasty on the interdigestive myoelectrical complex of the stomach. *Gut*. 1972; 13(10): 841-2.

[13] Takahashi T. Mechanism of interdigestive migrating motor complex. *J Neurogastroenterol Motil*. 2012; 18(3): 246-57.

[14] Nakajima H, Mochiki E, Zietlow A, et al. Mechanism of interdigestive migrating motor complex in conscious dogs. *Journal of gastroenterology*. 2010; 45(5): 506-14.

[15] Furness JB, Jones C, Nurgali K, et al. Intrinsic primary afferent neurons and nerve circuits within the intestine. *Progress in neurobiology*. 2004; 72(2): 143-64.
[16] Furness JB. The organisation of the autonomic nervous system: peripheral connections. *Autonomic Neuroscience: Basic and Clinical*. 2006; 130(1): 1-5.
[17] Furness JB, Callaghan BP, Rivera LR, et al. The enteric nervous system and gastrointestinal innervation: integrated local and central control. *InMicrobial endocrinology: The microbiota-gut-brain axis in health and disease*. Springer-New York: 2014.
[18] Bornstein JC, Costa M, Grider JR. Enteric motor and interneuronal circuits controlling motility. *Neurogastroenterology & Motility*. 2004; 16: 34-8.
[19] Brasseur JG, Nicosia MA, Pal A, et al. Function of longitudinal vs circular muscle fibers in esophageal peristalsis, deduced with mathematical modeling. *World J Gastroenterol*. 2007; 13(9): 1335-46.
[20] Smith TK, Robertson WJ. Synchronous movements of the longitudinal and circular muscle during peristalsis in the isolated guinea-pig distal colon. *The Journal of physiology*. 1998; 506(2): 563-77.
[21] Smith TK, Spencer NJ, Hennig GW, et al. Recent advances in enteric neurobiology: mechanosensitive interneurons. *Neurogastroenterology and motility*: the official journal of the European Gastrointestinal Motility Society. 2007; 19 (11): 869-78.
[22] Amar K. Ganguly, Anuva Ganguly. *Microprocessors and Microcontrollers: 8085, 8086 and 8051* (1st. ed.). Alpha Science International, Ltd, 2012.
[23] Rønnestad I, Akiba Y, Kaji I, et al. Duodenal luminal nutrient sensing. *Curr Opin Pharmacol*. 2014; 19: 67-75.
[24] Rasoamanana R1, Darcel N, Fromentin G, et al. Nutrient sensing and signalling by the gut. *Proc Nutr Soc*. 2012; 71(4): 446-55.
[25] Chandra Rashmi Liddle, Rodger A. Regulation of Pancreatic Secretion. *Pancreapedia: Exocrine Pancreas Knowledge Base*. 2015; DOI: 10.3998/panc.2015.38
[26] Chey William Y, Ta-min Chang. Neural hormonal regulation of exocrine pancreatic secretion. *Pancreatology*. 2001; 320-335.
[27] Wood J.D. Enteric Nervous System: Neuropathic Gastrointestinal Motility. *Dig Dis Sci.* 2016; 61: 1803-1816.
[28] Bornstein J. C. Enteric reflexes that influence motility. Innervation of the gastrointestinal tract. *CRC Press*. 2002: 21-76.
[29] Punati J, Bhardwaj V, Hurtado C. W, et al. *Gastrointestinal motility physiology*.
[30] Browning KN, Travagli RA. Central nervous system control of gastrointestinal motility and secretion and modulation of gastrointestinal functions. *Comprehensive physiology*. 2011; 4(4): 1339-68.
[31] Travagli RA, Hermann GE, Browning KN, et al. Brainstem circuits regulating gastric function. *Annu. Rev. Physiol*. 2006; 68: 279-305.
[32] Smeets, Paul AM, Alfrun Erkner, et al. Cephalic phase responses and appetite. *Nutrition Reviews*. 2010; 643-655.
[33] Mussa BM, Verberne AJ. The dorsal motor nucleus of the vagus and regulation of pancreatic secretory function. *Experimental physiology*. 2013; 98(1): 25-37.
[34] Kunze W. A. A, J. B. Furness. The enteric nervous system and regulation of intestinal motility. *Annual review of physiology*. 1999; 117-142.
[35] Browning KN, Verheijden S, Boeckxstaens GE. The vagus nerve in appetite regulation, mood, and intestinal inflammation. *Gastroenterology*. 2017; 152(4): 730-44.
[36] Babic T, Browning KN. The role of vagal neurocircuits in the regulation of nausea and vomiting. *European journal of pharmacology*. 2014; 722: 38-47.