FUNCTIONAL DISORDERS OF THE FOREGUT

ESSAY

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Master Degree in
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Presented by

Dr. Medhat Mohamed Mohamed

M. B., B. Ch. Faculty of Medicine
Ain Shams University

Under Supervision of

Professor Dr. Alaa Ismail

Professor of Surgery
Ain Shams University

Assisted In Supervision

Dr. Khaled Gawdat

Lecturer of Surgery
Ain Shams University

Faculty of Medicine
Ain Shams University

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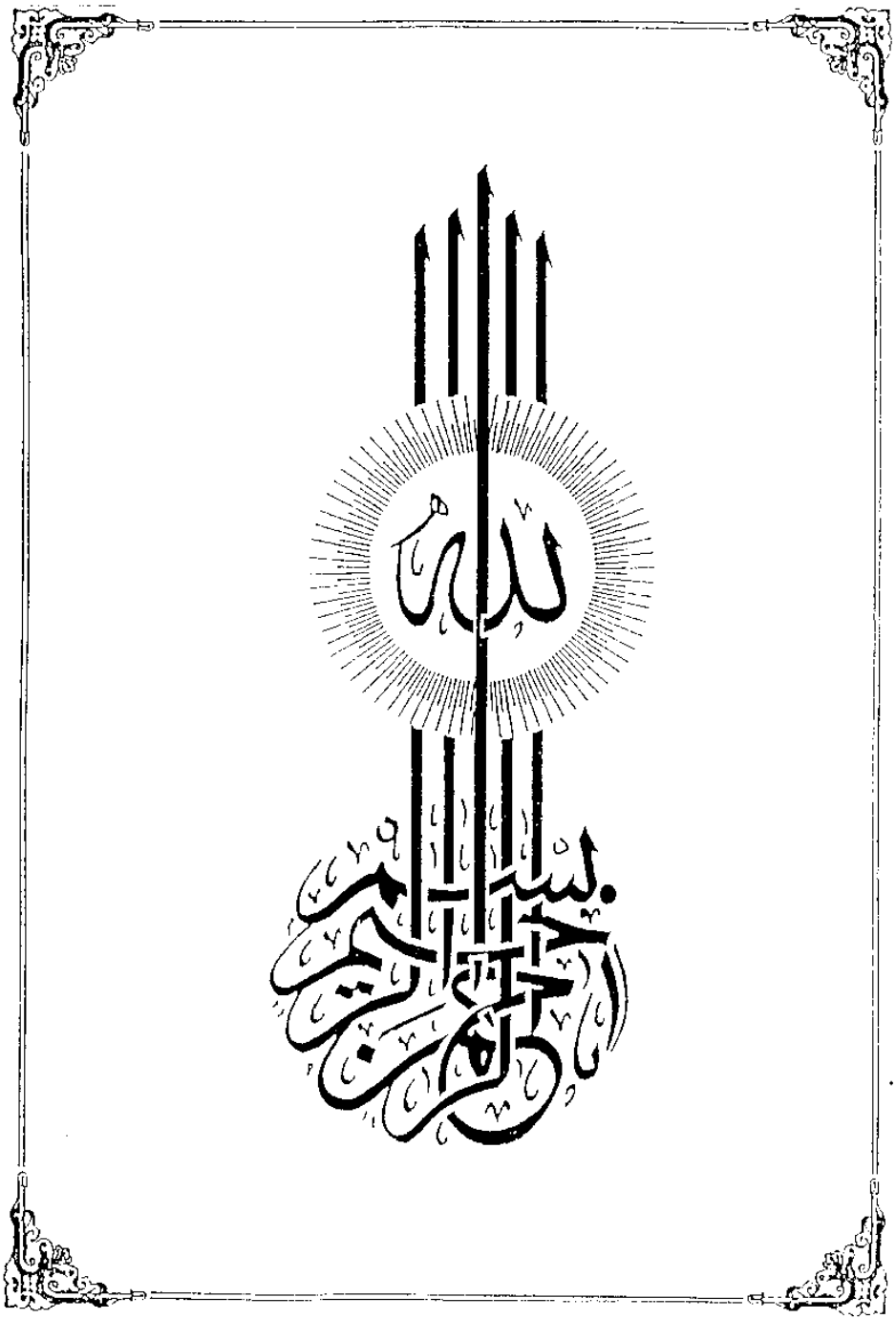

Dedication

To my mother, father and brothers. To the soul of my grandfather. To those doctors working for the sake of patient comfort and relief of suffering.

INTRODUCTION

INRODUCTION

The principle function of the digestive tract is the assimilation of nutrients; of the major processes contributing to this, two-exocrine secretion and intestinal absorption - are well understood, but the third, motility, is not.

In the absence of any clear understanding of "normal" motility. It is not suprising that most problems of "abnormal" motility are ill-defined. **(Wingate, 1984)**.Motility is controlled by three basic mechanisms : myogenic, neural and hormonal.Gastrointestinal motility disorders are quite common in clinical practice but are frequently disguised under such vague terms as non-ulcer dyspepsia, chronic gastritis, abdominal neurosis, vagus nerve dysfunction and the like. **(H. Abdel Hamid, 1993)**.

Motility disorders of the gastrointestinal tract can be intrinsic to the alimentary function or can result from surgical manipulation of the bowel or nervous system. **(Baker, 1993)**.

Our study will entail discussion of motility disorders of the foregut. With the advent of modern electrophysilogic, manometric and histologic techniques great achievements have been gained in the diagnosis and management of motility disorders. Intracellular recordings of electrical activity from muscle cells are recorded by use of electrodes that impale smooth muscle cells. **(Baurer et al., 1987)**.

The first insights into function of the stomach and small intestine were drived from radiologic studies,especially those of Cannon.From these studies came the currently held idea of the differing functions of the proximal and distal stomach. In the 1920s, Alvarez and Mahoney recorded electrical activity from the stomach and laid the foundations of gastric electrophysiology. Recently, the Malagelada group developed an innovative barostat system that has increased our understanding of the physiology of this region. **(Quigley, 1992)**.

Recoring of pressure from within the bile duct may indirectly reflect gross alterations in the sphincter of Oddi activity. **(Tanaka et al., 1990)**.

By achieving a better understanding of the relationship between normal and abnormal motor physiology to symptoms, future medical and surgical treatment should be less empiric, more specific and more effective. **(Becker, 1993)**.

AIM OF WORK

This work aims to review the most recent literature regarding foregut motility and its disorders.

The essay will include the following items :

1. Introduction.
2. Physiology of gastointestinal motility.
3. Pathology of gastrointestinal motility disorders.
4. Diagonsis and investigations of gastrointestinal motility disorders.
5. Treatment of gastrointestinal motility disorders.
6. Conclusion.
7. English summary.
8. References.
9. Arabic summary.

PHYSIOLOGY

INTRODUCTION

The term "motility" really encompasses a number of events:(1) Myogenic events in the smooth muscle cells (myocytes) leading to contractions; (2) Neurogenic events, which coordinate smooth muscle contraction by both intrinsic and extrinsic nerves; (3) Coordinated smooth muscle contractions, which lead to elevated intraluminal pressure; and (4) Propulsion, which is the net result of events 1 through 4 (Phillips, 1990) .

MOTOR ANATOMY OF THE DIGESTIVE TRACT

Morphologically, the most important characteristic of gastrointestinal smooth muscle is the arrangement of cells within layers in a syncytium, as in the myocardium. Adjacent cells are connected by "nexuses" or gap junctions, permitting the spread of electrical activity from one cell to another to allow coordinated movement of the muscle mass, which is potentially independent of neural control (Wingate, 1984).

Gastrointestinal sphincters are specialized circular muscles that ensure the timely delivery of luminal contents from one visceral organ to the next, so that each may perform its task efficiently. (Szurszewski, 1987). Sphincters also block the retrogarde flow of contents from one organ to the other (Goyal and Paterson, 1987).

Within the gut wall, there is a population of non-neural non-muscle cells (neuronoid cells) located between the longitudinal and circular smooth muscle layers called interstitial cells of Cajal (Thunenberg, 1982). They are only identified with electron microscopy. They serve a dual function as regards motility. They are believed to be the pacemakers of the gut and are believed to secrete the final nonadranergic noncholinergic (NANC) inhibitory neurotransmitter nitric oxide which causes active relaxation. Nitric oxide

(No) is probably released by these cells in response to vagal stimulation, with the neurotransmitter released by vagal nerve endings being VIP. Interstitial cells of Cajal possess VIP receptors on their surface. It is hypothesized that the receptive (adaptive) relaxation of the proximal stomach is caused by nitric oxide through the intermediary role of VIP, while the receptive relaxation of the lower oesophageal sphincter is caused by VIP directly (H. Abdel Hamid, 1993)

I-NERVOUS CONTROL OF MOTILITY

Nervous control of motility may be extrinsic (through the sympathetic and parasympathetic divisions of the autonomic nervous system as well as voluntary motor fibres to the upper and lower ends of the gastrointestinal tract) or intrinsic. The function of the extrinsic nerve supply is not to initiate activity in the muscle but rather to modify it. (Ganong, 1993).

Extrinsic innervation may be afferent or efferent, while intrinsic innervation is provided by the myenteric plexus.

I- Extrinsic Innervation:

(1) Afferent Nerve Fibres:

Vagal primary afferent neurons constitute 80% of vagal fibres and travel rostrally, in the medulla as the solitary fasciculus (Chernicky, 1984), with the cell bodies located at the nodose ganglion of the vagus (Mei, 1985).

Splanchnic primary sympathetic afferent neurons constitue 20% of fibres with their cell bodies located segmentally in dorsal root ganglia of the spinal cord from T_2 through S_3 (Neuhuber, 1982). They may carry pain sensation (Ranieri et al., 1973).

(2) Efferent Nerve Fibres:

The extrinsic nervous system fine tunes spontaneous motility patterns by modulating the intrinsic myenteric nervous system through excitatory

(parasympathetic) and inhibitory (sympathetic) pathways. The oesophagus and anus are the only portions of the G.I.T. under any extrinsic voluntary control (Zenilman, 1993). These portions contain striated muscles supplied by excitatory alpha motor neurons, with acetylcholine being the transmitter released at the motor end plate (special visceral efferent outflow). Sympathetic and parasympathetic innervation comprise the general visceral outflow (Goyal, 1987).

Sympathetic efferent stimulation generally causes inhibition of gastrointestinal motor and secretory activity, and contraction of gastrointestinal sphincters and blood vessels (Szurszewski, 1981). Electrical vagal efferent stimulation, in general , produces excitatory as well as inhibitory effects. After blockade of cholinergic (muscarinic) excitatory influences, vagal stimulation usually produces inhibition or inhibition followed by excitation. Both of these responses (i.e., inhibition or inhibition followed by excitation) are mediated by noncholinergic transmitters (Goyal, 1987). Most preganglionic parasympathetic neurons are cholinergic. However, some vagal parasympathetic neurons contain catecholamines (Gwyn et al., 1985) and enkephalins (Lundberg et al., 1978). The postganglionic neurons of the parasympathetic system are probably part of the myenteric plexus (Guyton, 1990). The sympathetic preganglionic neurons are primarily cholinergic but some also contain enkephalins (Falsgaard et al., 1982). It has been suggested that enkephalins may act as presynaptic inhibitors of acetylcholine release from presynaptic terminals (Konishi, 1979). Most postganglionic neurons are adrenergic and inhibitory in nature (Ganong, 1993).

II-Intrinsic Innervation (The Enteric Nervous System)

The most remarkable feature of the innervation of the gut is its own intramural neurons system, called the enteric nervous system, or the "minibrain" of the gut, which is quite complicated and contains nearly as many neurons as the CNS (Telford and Szurszewski, 1985). The enteric nervous system is capable of functioning independently of any extrinsic innervation or central nervous system control, but its function can be

modulated by the CNS by means of sympathetic and parasympathetic efferent nerves that are connected to enteric neurons. Although it is not known with certainty, some of the final motor neurons in the enteric nervous system may also be the second order (postganglionic) neurons in the parasympathetic pathway (Goyal, 1987).

The enteric neurons are arranged in the form of plexuses. There are two main enteric plexuses which are the myenteric and submucous plexuses. The myenteric plexus controls mainly gastrointestinal motility which is our concern in this study, while the submuscosal plexus controls secretions and also subserves many sensory functions (Guyton, 1990).

The enteric nervous system provides moment-to-moment control of contractile activity. Neural isolation from the CNS by direct neurotomies or by autotransplantation of the small intestine has only a minor effect on the orderly propulsion of chyme (Sarna and Kelly, 1981). The intrinsic nervous system is especially responsible for many local gut neurogenic reflexes (Guyton, 1990). The peristaltic or myenteric reflex is a classical enteroentecic reflex that reflects the coordinated circuitry of the enteric nervous system (Miedema et al., 1992), with descending inhibition and ascending excitation that is subject to extrinsic modulation by facilitation or inhibition (Otterson et al., 1993).

Neurotransmitters of the digestive tract are adrenergic (inhibitory), cholinergic (excitatory), and nonadrenergic noncholinergic (NANC).

Examples of the latter include VIP, the tachykinins (substance P and substance K) , and ATP. Peptides such as gastrin, histamine, serotonin, GABA, neuropeptide Y, peptide YY, opioids, galanin, motilin and CCK all have measurable effects on intestinal motility and are probable neurotransmitters, although the physiological roles of each are still being worked out (Zenilmann, 1993). Acetylcholine, bombesin-like peptide and substance P are candidates as excitatory neurotransmitters, while most of the actions of ATP, calcitonin gene-related peptide, galanin and VIP are inhibitory in nature(Goyal, 1989). Nitric oxide (No) recently has been given much attention as a potent nonadrenergic noncholinergic mediator of muscle relaxation (Bult et al., 1990). Deficiency of nitric oxide synthetase from the gut has been linked to the development of pyloric dysmotility, specifically,

infantile hypertrophic pyloric stenosis (Vanderwinden et al., 1992). Some previously identified inhibitory neurotransmitters such as ATP and VIP may act with nitric oxide with the latter being the final mediator (Otterson and Sarr, 1993).

Table 1-1. NEUROTRANSMITTER CANDIDATES

Low-Molecular-Weight Substances
Acetylcholine
Biogenic amines
Catecholamines
Dopamine
Norepinephrine (NE)
Epinephrine
Tyramine
Octopamine
5-Hydroxytryptamine (5HT)
Products of general metabolism
Amino acids
Glycine
Gamma-aminobutyric acid (GABA)
Glutamate, aspartate
Purines
Adenosine triphosphate (ATP)
Adenosine
Neuropeptides
Bombesin-like
Cholecystokinin (CCK)
Calcitonin gene-related peptide (CGRP)
Galanin
Neuropeptide Y (NPY)
Dynorphin
Enkephalin (Leu, Met)
Beta-endorphin
Somatostatin
Substance P (SP)
Vasoactive intestinal peptide (VIP)

From Goyal RK and Crist JR : Neurology of the gut. *In* Sleisenger/ Fordtran : Gastrointestinal Disease, 1989, p.27 .

It appears that the function of enteric nerves is to convert the uncontrolled and purposeless motor and secretory activity of the gut into purposeful and coordinated intestinal activity. The enteric nerves serve in generating propulsive activities such as peristalsis and other propagated motor complexes including the migrating motor complex. They also

generate reverse peristalsis , modulate segmental contractions , and coordinate activities of the gastrointestinal sphincters. The net effect of enteric nerves on the circular muscle layer is inhibitory in nature. Hence , in the total absence of enteric nerves , myogenic contractions of the small bowel increase in frequency (as they are generated by myocytes) , but they lack orderly propagation (Goyal, 1989). The role of enteric nerves in the control of gut functions can be appreciated by their experimental blockade by tetrodotoxin (a neurotoxin that blocks conduction of all spike activity in nerves) and clinically by the observation of near complete loss of enteric neurons in disease states such as achalasia (Heuser, 1979) , Hirschsprung's disease (Rothman et al., 1989) and some cases of the intestinal pseudo-obstruction syndrome that may involve enteric neurons (Schuffler, 1982). In these cases , in the absence of any neural input , the only motor activity that remains is that controlled by hormonal influences or intrinsic activity of muscle or secretory cells.(Goyal,1989).

II- MYOGENIC CONTROL OF MOTILITY

The cardinal characteristic of gastrointestinal smooth muscle is its spontaneous electrical rhythmicity, in which it resembles myocardial smooth muscle (Wingate, 1984). The myocyte cell membrane exhibits rhythmic spontaneous, slow low amplitude depolarizations or oscillations of muscle membrane potential called "slow waves" (Tomita, 1981). They are also called "electrical control activity" (ECA), or "basic electrical rhythm", BER (Zenilman, 1993). The frequency of their recurrence, while relatively constant for any organ, varies from 3 cycles per minute in the stomach to 12 cycles per minute in the duodenum. They propagate over varying lengths of bowel from their site of origin (Conklin, 1989). They are generated by the interstitial cells of Cajal present at the boundary between the longitudinal and circular smooth muscle layers of the small bowel (Suzuki et al., 1986). Spike potentials (action potentials) may be superimposed upon them with production of muscle contraction. Unlike cardiac muscle, not all waves are

followed by mechanical contraction, thus,electromechanical coupling may be complete or incomplete (Wingate, 1984).Unlike the myocardium, pacemakers are found in the gut. These are areas with the highest slow wave cycle rate and are proximally situated. They thereby entrain and drive more distally situated areas with slower slow wave cycle rates. They are therefore considered to be the pacesetters of more distal regions. In the stomach, a gastric pacemaker is found along the greater curvature nearly at the junction of the upper and middle portions of the corpus. In the duodenum, another pacemaker is found just distal to the pylorus at the point of entry of the common bile duct. The gastric pacemaker discharges at a rate of 3 cycles / minute, while the duodenal pacemaker discharges at a rate of 12 cycles / minute. (Zenilmann, 1993). A pacesetter potential has also been described in the sphincter of Oddi. Although short, the sphincter can be anatomically divided into proximal and distal portions. Myocytes of the proximal sphincter myoelectrically drive the cells of the distal sphincter at a rate of 12 to 15 cycles per minute (Shearin et al., 1984).

Transection of the small bowel interrupts the caudal propagation of slow waves from the duodenal pacemaker, and the muscle immediately distal to the transection then assumes the role of pacemaker for the remaining length of bowel (Wingate, 1984).

When compared with striated muscle, two of the most striking features of smooth muscle contraction are its economy of energy utilization and slowness. (Warshaw et al., 1983).

Neurohormonal agents affect contractility by depolarizing or hyperpolarizing the membrane, or changing the duration, amplitude, or number of action potentials and thereby affect the force and duration of contraction (Sims et al., 1985).

Different gastrointestinal muscles are characterized by different force-length relationships in the unstimulated state. For example, sphincteric muscles generate a much steeper force-length curve than circular muscles from adjacent organs. The steeper force-length curves of unstimulated muscle occur because the contractile machinery of the sphincter muscle is partially and continuously activated through some intrinsic myogenic system (Christensen, 1973). That is, the sphincter is tonically contracted as a result