Electromyography of the sphincter of Oddi and gastrointestinal tract : experimental studies in the Opossum

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Promotores: Prof. Dr. J.M. Greep, Maastricht
Prof. Dr. F.G. Moody, Houston, USA

Referenten: Prof. Dr. J.A. Flendrig, Maastricht
Prof. Dr. G.N. Tytgat, Amsterdam
Prof. Dr. P.J. Kloppe, Amsterdam

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This thesis is dedicated with love to my wife, Celia Regina, and my two daughters, Caroline and Christine.

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CHAPTER 1

GENERAL INTRODUCTION

The gastrointestinal tract has the important function of converting food into smaller constituents and absorbing them. In order for these events to be achieved, food must be mixed with digestive juices and transported along the alimentary tract at an appropriate rate.

1.1. HISTORICAL BACKGROUND

Motility of the gastrointestinal tract has fascinated man for centuries. The earliest description of movements of the stomach was made by Haller in 1764, who observed that contraction of the stomach alternated with relaxation in vivisected wolves, dogs, and cats (1). In 1833, Beaumont observed movements of the stomach directly through an accidentally created gastrostomy in a man who had been wounded in the epigastrium by the accidental discharge of a musket (2). He described the important functions of the pylorus in regulating the passage of gastric contents from the stomach into the duodenum as well as impeding the regurgitation of duodenal secretion. Several other

investigators, including Friedman, Bassow, Blondlot, Quincke, and Pavlov, also made important contributions to our knowledge of gastric physiology using gastric fistulas and pouches (3).

Contraction of the small bowel was studied by exteriorizing the gut or placing it in the subcutaneous tissue. Some of these methods are still employed (4-6). In the Thiry-Vella technique, the stomas of a sectioned segment of the small bowel are exteriorized through the abdominal wall. The continuity of the remaining small bowel is re-established. This enables the placement of a small recording balloon into the gut. The small bowel can also remain in continuity and be placed within a tube of skin (Biebl loop) or on the top of the skin.

Motility of the gut has also been studied in vitro. In 1854, Haffter appears to have been the first to have evaluated peristalsis in excised segments of the small bowel in a warm water bath with oxygenated Locke solution (3). In 1904, Magnus evaluated the effect of pharmacologic substances on resected gut (3). This eliminated the action of the extrinsic nerves on the bowel.

From 1898 to 1914, Cannon made many contributions to the knowledge of gastrointestinal motility employing the newly discovered x-ray to study the peristalsis of the esophagus, stomach, and bowel (7-9). He described peristaltic contraction rings pressing the gastric contents through the pylorus. Radiographic techniques had the

advantage that movement of radiopaque substances within the gastrointestinal tract could be evaluated in conscious animals. However, overlying loops of the intestine was a drawback of this technique.

In 1920, Wheelon and Thomas concluded that the pyloric sphincter was not an independent muscular structure but contracted rhythmically in coordination with the antrum of the stomach (10). In 1921, Alvarez performed the first electromyography of a human stomach by placing the electrodes on the skin of a patient with a large ventral hernia in the left upper quadrant of the abdomen (3,11). In 1922 Alvarez demonstrated in dogs and in rabbits that a slow wave precedes each contraction and that not all slow waves were accompanied by contractions (12). With the improvement of electronic recorders in the following years, many animals studies followed Alvarez's marvelous work.

The relationship between slow waves, spike potentials, and contractions is now well established. In 1969, Szurszewski demonstrated in the fasted dog a specific myoelectric migrating complex (MMC) which migrated down the gastrointestinal tract cyclically from the stomach to the terminal ileum (13). In 1975, Code and Marlett divided the MMC into four phases (14). During phase I, occasional or no spike potentials are observed. In phase II, spike potentials are superimposed on the slow waves in a random fashion. Phase III consists of spike potentials of high amplitude on each slow wave. During phase IV, the frequency and amplitude

of spike potentials decrease rapidly to begin a new MMC. Feeding interrupts the MMC and results in a noncyclical pattern of intermittent spike potentials that persists for the duration of the postprandial period. Following these initial descriptions of the MMC, numerous studies have been performed to evaluate the myoelectric activity of the gastrointestinal tract under several conditions and in several species. The MMC is further discussed in section 6 of this Chapter.

A great deal of our knowledge about the motor activity of the alimentary tract is founded on interpretation of the structure of the musculature and its nerves. The musculature, innervation, and neuromuscular junction of the gastrointestinal tract is also reviewed in this introduction.

1.2. SMOOTH MUSCLE OF THE GASTROINTESTINAL TRACT

The muscle coat of the gastrointestinal tract is a continuous structure made of smooth muscle and extending from the esophagus to the anal canal. Except in the stomach, the muscle cells of the gastrointestinal tract are grouped in two layers termed outer longitudinal layer and inner circular layer. The wall of the stomach is composed of three muscular layers, inner oblique, middle circular, and outer

longitudinal layer. Although the circular and the longitudinal layers are separated by the myoenteric plexus, they are linked to each other by connective tissue bridges (15). These bridges have been implicated as the means of communication between the two layers.

At the connection between different segments, a sphincter may be formed by the localized thickening of the circular layer, such as the pylorus and the sphincter of Oddi. Occasionally, the sphincteric function of a segment is not due to the thickening of the muscular layer, but is due to the fine structural features of the innervation and pharmacological characteristics of the musculature of that portion of the gastrointestinal tract. This peculiar segment is observed at the esophagogastric junction and is termed a physiologic sphincter. The sphincters in the alimentary tract have two important functions; to regulate the velocity of emptying of the proximal segment into the distal as well as to impede the regurgitation of contents from the distal segment.

The muscle cells of the gastrointestinal tract are uninucleated, spindle-shaped, and measure 500 to 700 μm in length and 2 to 10 μm in thickness at rest (16). During contraction, the muscle cells can shorten to less than one-fourth of their initial size. They have a high surface/volume ratio and they form a network with intermeshed collagen fibers. The surface of the cells contains several specialized structures that establish

junctions between adjacent cells and junctions between a cell and the surrounding connective tissue stroma (17). These junctions are of paramount importance for transmission and propagation of action potentials between the cells. Since the myosin and actin filaments are not regularly arranged, smooth muscle cells lack the striation typical of cardiac and skeletal muscle.

The smooth muscle cells contract by sliding of myofilaments toward and over one another, i.e., the actin filaments are pulled inward among the myosin filaments so that they overlap each other to a major extent (18).

Initiation of muscle contraction starts with action potentials in the muscle fibers. These potentials of action spread to the interior of the fiber where they cause release of calcium ions from the sarcoplasmic reticulum. Then the calcium ions initiate the chemical events of the contractile process. Finally, contraction occurs after depolarization of the membrane and stops after repolarization.

The smooth muscle of the gastrointestinal tract exhibits two types of myoelectric activity, referred to as slow waves and action potentials (19). Slow waves are myogenic, spontaneous, and secondary to regular depolarization (10 to 15 mV) and repolarization of the smooth muscle cells. They are generated in the longitudinal muscle layer and possibly spread to the circular layer (20). All points in a cross-section of the gastrointestinal tract are in phase and each segment of the gastrointestinal tract

generates a slow wave frequency typical of that segment. In the opossum small intestine, for example, the slow wave frequency decreases linearly from the duodenum, where the frequency is about 19 cycles/min, to about 14 cycle/min in the terminal ileum. This phenomenon is called the slow wave frequency gradient (21). The slow wave frequency is 3.5/min in the stomach and 19/min in the sphincter of Oddi of the opossum.

The cause of the slow wave rhythm is as yet unknown. It has been suggested that it may be caused by rhythmic activity of an electrogenic sodium pump (18). The slow waves are always present and they determine the timing and maximal frequency of contractions. Therefore, the slow waves are frequently called pacemaker waves. They do not cause muscle contraction, but when the potential of the slow waves rises above the level of approximately -35 mV, an action potential develops and contraction ensues. Such action potentials can be elicited in many ways, such as by electrical stimulation, action of hormones, neurotransmitters, or by spontaneous generation in the muscle fiber.

Unlike slow waves, action potentials do not usually occur continuously. They can occur alone or in bursts and are followed by a weak or strong contraction of the circular and longitudinal muscles (22,23). Since action potentials are superimposed on the depolarization of the slow waves, the slow wave frequency determines the maximum frequency of contraction. For example, in the opossum stomach, four

contractions per minute is the maximum, while in the duodenum and sphincter of Oddi, the maximum frequency of contractions is 19 per minute.

Once an action potential starts, it spreads through the entire muscle mass. This creates a constrictive ring in the gastrointestinal wall which moves and propels the intestinal contents downward. This process is called peristalsis. The slow wave propagation velocity determines the velocity of peristaltic contraction (24).

Although the contractile process in smooth muscle is similar to that in skeletal muscle, some important differences exist. The contraction and relaxation time of smooth muscle is longer than in skeletal muscle (18). For this reason, smooth muscles are especially well suited for maintaining prolonged contraction without fatigue and with little energy consumption.

Another special characteristic of the smooth muscle is its ability to shorten a far greater percentage of its length than can skeletal muscle (18). This allows the gastrointestinal tract to change its lumen diameter several times. Due to the random arrangement of the actin and myosin filaments in smooth muscle, it has the ability to greatly change its length with minimal variation of the tension. This feature is of special importance in the stomach, whose lumen may change dramatically after a meal.

1.3. INNERVATION OF THE GASTROINTESTINAL TRACT

The alimentary tract is innervated by both the parasympathetic and sympathetic nervous systems that are capable of changing the activity of specific segments or the entire alimentary tract.

The parasympathetic fibers that supply the gut originate from the vagal motor nucleus in the medulla oblongata (cranial division) and from the second, third, and fourth sacral segments of the spinal cord (sacral division) (25). The cranial parasympathetic division is transmitted by the vagus nerves and innervates the gut from the esophagus to the right colon, including the gallbladder. The sacral division passes through the pelvic nerves to the left colon, rectum, and internal anal sphincter and has an essential role during defecation.

The sympathetic fibers to the alimentary tract originate in the spinal cord between the segments T-8 and L-3 and, after passing the celiac, superior mesenteric, inferior mesenteric, or pelvic ganglia, they are distributed with the blood vessels to the gut (25).

The great majority of neurones and fibers to the gastrointestinal tract are grouped in two plexuses named myenteric or Auerbach's plexus and submucosal or Meissner plexus (26,27). They extend along the entire length of the smooth muscle wall from the esophagus to the anus. The myenteric plexus is mainly motor in function and lies

between the longitudinal and circular muscular layers. Most myenteric fibers are stimulatory (cholinergic) but some are probably inhibitory (adrenergic).

The submucosal plexus, which is localized in the submucosa, has the important function of receiving stimulus from the gut mucosa and from stretch receptors in the gut wall (28). These stimuli are conveyed by sympathetic and parasympathetic nerves. Painful stimuli are transmitted to the spinal cord by sympathetic fibers while signals that initiated several gastrointestinal reflexes are propagated to the medulla oblongata via the vagus nerve.

The dominant effect of the stimulation of the vagus nerve on the muscle of the small intestine and proximal colon is excitatory (29,30). If the intestine is quiescent, rhythmic contractions are initiated, and if the gut is in contraction, the existing contraction increases in amplitude. The excitatory effects of the pelvic nerves are more prominent in the distal colon and rectum, but the proximal colon and even the distal ileum may also respond with some delay. Therefore, there is an overlapping of innervation of the vagus and pelvic nerves. The pelvic nerves contract both the circular and longitudinal muscle layers of the colon and rectum that are involved with defecation (31).

The action of the sympathetic pathways on the movements of nonsphincteric parts of the intestine is inhibitory, while the sympathetic innervation of the sphincters is

excitatory. It is also important to note that the presence of a few sympathetic excitatory as well as inhibitory vagal fibers to the nonsphincteric parts of the intestine have been documented by several authors (31).

1.4. NEUROMUSCULAR JUNCTION OF THE GASTROINTESTINAL TRACT

Although there is no specialized neuromuscular junction in the gut, transmission from intrinsic excitatory and inhibitory neurons is very effective and even a single nerve pulse elicits either transient depolarizations or hyperpolarizations of the muscle cells (31,32). Bundles of axons with dilations or varicosities lie within the muscular layers of the gut. These varicose axons release transmitters when stimulated at many points adjacent to different muscle cells. These cells may also transmit the stimulus to several other muscle cells that are interconnected both electrically and mechanically.

1.5. ANATOMY AND INNERVATION OF THE SPHINCTER OF ODDI

According to Boyden, Glisson was the first to observe the "locking mechanism" of the sphincter of Oddi that

consists of "ringlike fibers which occupy not only the opening (of the common channel) itself but also the whole oblique tract (through the intestinal wall)" (33). Gage was the first to examine the sphincter of Oddi microscopically (34). This sphincter was named after the Italian Oddi, who was the first to demonstrate it in several animals, to measure its resistance, to postulate that its dysfunction might cause clinical symptoms, and to show that removal of the gallbladder caused marked dilatation of the bile ducts (33,35).

The distal common bile duct passes downward behind the first part of the duodenum and within the head of the pancreas. The duct then curves to the right to course obliquely through the duodenal wall for a distance of 8 to 22 mm (36). In approximately 80% of the instances, the main pancreatic duct joins the posteromedial aspect of the common bile duct to form a common channel, which is referred to as the ampulla of Vater, although there is no dilatation of the channel (37). The common bile duct and the main pancreatic duct, either together or separately, pierce the second portion of the duodenum at a smooth elevation of the mucosa, named major papilla.

Boyden has demonstrated that the sphincter of Oddi in humans is formed by the sphincter choledochus and the sphincter ampullae that encircles the distal common bile duct and the ampulla of Vater, respectively (33). In some human specimens, a band of thickened muscle, the sphincter

pancreaticus, surrounds the end of the pancreatic duct (33).

Only a few studies have been reported on the innervation of the sphincter of Oddi. Kyosola has demonstrated, in cats and dogs, that the ganglia of the myenteric and submucosal plexuses in the sphincter of Oddi are rich in cholinergic fibers (38). Adrenergic fibers may also innervate the sphincter of Oddi (39). Toouli et al. showed that the density of ganglia is larger at the proximal segment of the sphincter of Oddi of the opossum (40). They suggest that the higher density of ganglion cells in the proximal portion of the sphincter may constitute a center of neural modulation of sphincter function.

1.6. MOTILITY OF THE GASTROINTESTINAL TRACT AND SPHINCTER OF ODDI

The progression of food from the stomach to the rectum is complex and involves secretion and mixing of digestive juice with nutrients and absorption and transporting of the gut contents at an appropriate rate. The luminal contents undergo dramatic changes in volume, in physical state, and in chemical composition as they progress through the digestive tube. Therefore, it is not surprising that the pattern of motility of the gut varies with feeding habit, volume and composition of the diet, the fasted or fed

states, the different parts of the intestine, and with different species.

The generally recognized movements of the gut are peristalsis, segmentation, and pendular movement (18). Peristaltic waves may occur in any part of the intestine and consists of one or more contractions of the circular muscle that are propagated along the bowel. This provides a constricting ring that propels the content analward along the gut. This movement is mainly propulsive, although some content mixing may also occur.

Segmentation movements consist of two or more simultaneous concentric contractions of small segments of the gut. The segmentation contractions have a brief duration and as one set of contractions relaxes, a new set begins. In this way, the segments are constantly divided and subdivided. This results in progressive mixing of food particles with digestive juice.

Pendular movements consist of contractions and relaxations of the longitudinal muscle of the gut that result in shortening and lengthening of intestinal segments in a pendular fashion. These movements are poorly understood since they cannot be adequately evaluated by electromyography, pressure change within the bowel lumen, or by deformation of strain gauge transducers attached to the gut wall (41). Peristalsis and segmentation are movements of circular muscles and are effectively studied with methods mentioned above.

Change in contractions of the muscularis mucosae can cause shortening or lengthening of the intestinal mucosa folds which decreases or increases the exposed mucosa to the chyme and the rate of nutrient absorption (18).

Early investigators were concerned mainly with the type and frequency of gut contractions that occurred over short periods of time. However, it was known at that time that the activity of the bowel was not uniform over long periods. Boldyreff was the first author to document that the motility of the gut was cyclic in the dog (42). He recognized that it was organized in brief bursts of activity which recurred at regular intervals of approximately 90 minutes and was interrupted by feeding.

In 1969, Szurszewski further characterized this recurrent pattern of gastrointestinal activity in dogs using an electromyographic technique (13). He described a sequence of myoelectric activities in which a period of approximately 60 minutes of no spike potentials was followed by a period of 15 to 40 minutes of irregular spike activity in the gut. This was followed by a four- to eight-minute period of intense spike activity. This sequence of activities started in the duodenum and migrated distally to the terminal ileum every 115 to 183 minutes.

Code and Marlett called this activity pattern the migrating myoelectric complex (MMC) and divided each complex into four phases (14). In phase I, occasional or no spike potentials occurred. During phase II, the spike potentials

were irregular and increased in frequency and intensity throughout the phase. Phase III was characterized by action potentials of high amplitude that were superimposed on 90 to 100% of the slow waves. During phase IV, the frequency and intensity decreased quickly to start a new cycle.

The MMC has been recorded only during the fasting state in some species and during fasting and fed states in others. Man, dog, cat, rat, and opossum are included in the first group (40,43,44), and sheep, cattle, rabbits, and pigs in the second group (45,46). Feeding interrupts the MMC in the first group of animals and results in a noncyclical pattern of intermittent spike potentials that persists for the duration of the postprandial period.

The correlation between the MMC phases and movements of intraluminal contents has been the objective of several studies. Code and Schlegel have demonstrated by combined cineradiographic and electromyographic recordings that the activity front of each complex (phase III) is associated with propagated contractions whose function is propulsion of gastrointestinal content between meals (47). They observed that any material injected into the lumen of a bowel loop during phase III was immediately propelled distally. The material was stationary when administered during phase I. Bueno et al. obtained similar results when nonabsorbable markers were radioscopically followed through the intestine of dogs and sheep (46).

It has also been suggested that the MMC is important

during the fasting state to prevent bacterial overgrowth of the small bowel. Vantrappen et al. reported that of 12 patients with possible bacterial overgrowth of the small intestine, five had gross disorders of the MMC patterns (48). In fact, disorders associated with abnormalities of the intestinal transit, such as diarrhea and intestinal pseudo-obstruction, present with changes of the gut myoelectric activity pattern (49).

Several studies have been conducted to describe the dynamics of the sphincter of Oddi. The methods most commonly employed are cholangiography, cineradiography, measurement of bile duct flow, choledochal pressure profilometry and manometry of the sphincter of Oddi and pancreatic and biliary ducts (50-54). Nuboer suggested in 1928 that the sphincter of Oddi presents peristaltic contractions and acts as an ejaculation apparatus (55). This hypothesis was supported by choledochal pressure profilometry studies performed by Bruijnes and Kloppe in dogs (56).

Recently, electromyography has been employed to evaluate the motility of the sphincter of Oddi. This method is advantageous over other studies because it can be employed in chronic studies on conscious animals. In addition, administration of fluids or placement of catheters in the pancreatic and biliary ducts is not necessary. Ishioka demonstrated in 1959 that the rabbit sphincter of Oddi generates spontaneous rhythmic bursts of spike potentials (57). In 1968, Ono detected periodic bursts of

spike potentials in the human sphincter of Oddi at laparotomy (58). Myoelectric recordings performed by Becker et al. and Honda et al. in 1982 revealed that the opossum sphincter of Oddi exhibits spontaneous spike potentials which propagated from the proximal to the distal portion of the sphincter (59,60).

Opossums are mammals of the family Didelphidae and superorder Marsupialia (Figure 1). They are omnivorous and usually live in hollow trees. The opossum was selected for the studies reported in this thesis because its sphincter of Oddi is mostly extraduodenal and measures 2 to 3 cm in length and, therefore, dissection of the pancreas and duodenum is not necessary to implant electrodes along the sphincter of Oddi. In addition, in the opossum, as in the human, the main pancreatic duct joins the common duct at the proximal portion of the sphincter of Oddi. The motility of the gastrointestinal tract is similar in the opossum and in the human. These animals also lie quietly for many hours without the need of drug administration or use of restraints.

1.7. OBJECTIVE OF THE PRESENT THESIS

This thesis consists of ten chapters. In Chapter 1, General Introduction, an historical background of the

Figure 1. Opossum during a recording session.

development of the motility of the gastrointestinal tract, a review of the anatomy and physiology of the smooth muscle, innervation, and neuromuscular junction of the gastrointestinal tract, anatomy and innervation of the sphincter of Oddi, motility of the gastrointestinal tract and sphincter of Oddi, and the objective of the present thesis are presented.

Eight experimental studies are described in Chapter 2 through 9. Initially, the normal electromyographic activity of the gastrointestinal tract and sphincter of Oddi is presented in Chapter 2. In this study, a new experimental model is also reported to measure the pancreatic duct and the common bile duct pressures under circumstances which minimally disturb the normal physiology of the pancreas, biliary tree, and sphincter of Oddi. In addition, the data obtained are used to correlate the pancreatic duct and biliary duct pressures with the sphincter of Oddi myoelectric activity, both in fasting and fed states.

The effect of different foods on the myoelectric activity of the sphincter of Oddi and gastrointestinal tract is evaluated in Chapter 3. Simultaneous gallbladder pressure recordings were also obtained in this study.

The effect of gastrointestinal hormones and acetylcholine on the sphincter of Oddi and duodenum myoelectric activity on pancreatic duct and common bile duct pressures is studied in Chapter 4.

Following studies of the electromyography of the

gastrointestinal tract and sphincter of Oddi under physiological conditions, the effect of abdominal operations and substances known to cause disturbances in the motility of the alimentary tract are evaluated. In Chapter 5, the motility of the gastrointestinal tract and sphincter of Oddi, both in the fasting and fed states, is studied following several abdominal operations.

The effect of alcohol on gastrointestinal and sphincter of Oddi myoelectric activity and on pancreatic and biliary duct pressures is described in Chapter 6. The mechanism by which ethanol stimulates the motility of the sphincter of Oddi and gastrointestinal tract is evaluated in Chapter 7.

The effect of two substances known to cause diarrhea is also studied. 16,16 dimethyl prostaglandin E_2 , a substance employed experimentally in the treatment of peptic ulcer disease, is evaluated in Chapter 8, and serotonin, a substance possibly responsible for the diarrhea in patients with carcinoid tumors, is studied in Chapter 9.

The final discussion is presented in Chapter 10.

The objective of this thesis is to study the motility of the sphincter of Oddi and gastrointestinal tract in conscious, nonmedicated opossums under physiological conditions and following several stimuli that cause gastrointestinal disturbances. The electromyographic activity of the sphincter of Oddi and gastrointestinal tract is correlated with the biliary and pancreatic duct pressures both in the fasting and fed states. The motility of the

sphincter of Oddi and gastrointestinal tract is evaluated following abdominal operations and following administration of different foods, gastrointestinal hormones, acetylcholine and substances known to cause diarrhea (prostaglandin and serotonin) and pancreatitis (alcohol). The mechanism of alcohol-related myoelectric activity disturbances of the sphincter of Oddi is also assessed.

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CHAPTER 2

A NEW METHOD FOR CORRELATING PANCREATIC AND BILIARY DUCT PRESSURES AND SPHINCTER OF ODDI ELECTROMYOGRAPHY

2.1. INTRODUCTION

Physiologic pancreatic and biliary duct pressures have been difficult to measure. Most commonly used methods of recording pressure produce either fistula, occlusion of a major duct by the recording catheter, or interference with the sphincteric mechanism (1,2,3). Recent developments in electrophysiologic techniques have allowed a more direct evaluation of the sphincter of Oddi (4). However, the correlation between electromyographic activity of the sphincter of Oddi and pancreatic and biliary duct pressures has not yet been evaluated.

A new experimental model has been developed to measure the pancreatic duct and common bile duct pressures under circumstances that minimally disturb the normal physiology of the pancreas, biliary tree and sphincter of Oddi. In addition, the data obtained was used to correlate pancreatic and biliary duct pressures with the sphincter of Oddi

myoelectric activity in conscious opossums, in both fasting and feeding states.

2.2. MATERIAL AND METHODS

Eight healthy opossums of either sex weighing 3.0 to 4.5 kg were studied. After an overnight fast, the animals were anesthetized with intraperitoneal administration of 25 mg/kg of sodium pentobarbital. The abdomen was entered through an upper midline incision.

The main pancreatic duct and the common bile duct were catheterized for pressure recording. A PE-50 polyethylene T tube was placed in the main pancreatic duct, 3 cm distal to its junction with the duodenum (Figure 1). The bile duct, which connects the right lateral lobule of the liver to the common duct below the cystic duct, was cannulated with PE-50 polyethylene tube.

Four bipolar extracellular electrode pairs were placed in the sphincter of Oddi and duodenum. Two pairs of electrodes were placed in the sphincter of Oddi: one pair was implanted 1 cm proximal to the sphincter of Oddi-duodenal junction and the second pair was placed 1 cm more distally. The third and fourth pairs of electrodes were placed in the duodenum, 2 cm proximal and 2 cm distal to the sphincter of Oddi-duodenal junction, respectively. The electrodes consisted of stranded silver-plated copper wire with teflon insulation of 36 AWG size. The biliary and

Figure 1. Schematic diagram of the opossum preparation shows the sphincter of Oddi and duodenum electrodes and the pancreatic and biliary catheters.

pancreatic catheters and the wires were passed through a subcutaneous tunnel to the animal's back and stitched to the skin. The wires were previously soldered to a female socket.

Recordings were begun 7 to 10 days after the operation. A male plug was inserted into the female socket, thereby conducting electromyographic potentials through isolation preamplifiers to an eight-channel Gould 2800S instrument (Gould Inc., Recording Systems Division, Cleveland, Ohio). Recordings were made by a paper speed of 1 mm/sec, low-frequency cutoff filter of 1 Hz, high-frequency cutoff filter of 10 Hz, and overall sensitivity of 100 mV.

The pancreatic and biliary catheters were attached directly to Gould P23 pressure transducers (Gould Statham Instruments, Inc., Hato Rey, Puerto Rico), which were connected to the Gould recorder. An Arndorfer hydraulic capillary infusion system (Arndorfer Medical Specialties, Inc., Greendale, Wisconsin) was used to administer water in the pancreatic and biliary ducts at a constant rate of 0.04 ml/min. The high-frequency cutoff filter was positioned at direct-couple offset.

Catheters equal to those placed in the pancreatic and biliary ducts were infused with water at a flow rate of 0.04 ml/min to determine the baseline pressure. The tip of each catheter was positioned externally at the same height as the internal catheters while the opossum was lying on its abdomen. To verify the sensitivity of the pressure system, the tip of each catheter was occluded for 2 seconds. This

caused an increase in pressure of at least 20 mm Hg.

Recording sessions of 5 to 8 hours were obtained in each animal for a period of 1 to 4 months, with an average of 10 recording sessions per opossum. The animals were studied in both the fasted and fed states. Ten to 20 g of commercial Purina cat chow, consisting of protein 30%, fat 8%, fiber 4.5%, moisture 12%, calcium 1.2%, phosphorus 1%, and NaCl 1.5%, were given before the sessions began or after recording two migrating myoelectric complexes.

For analysis of the myoelectric recordings, the migrating myoelectric complex in the duodenum was divided into four sequential phases, as suggested by Code and Marlett (5,6) and Carlson et al. (7). Phase I is the quiescent phase in which occasional or no spike potentials are observed. Phase II consists of irregular spike potentials that increase in frequency and intensity throughout the phase. Phase III is sudden in appearance and is characterized by regular spike potentials of high amplitude that accompanied 90 to 100% of the slow waves. During phase IV the frequency and amplitude of action potentials rapidly decrease to start a new myoelectric complex. The average number of spike potentials and the duration of each phase were determined. For recordings obtained after feeding, the average number of spike potentials in the sphincter of Oddi and duodenum was also calculated.

2.3. RESULTS

Myoelectric activity

Slow waves were easily identified in both the sphincter of Oddi and duodenum in most of the recordings. The frequency of slow waves was the same in the sphincter of Oddi and duodenum, and it varied from 17 to 20 per minute, with an average of 19 per minute. Inspection of the recordings revealed that the variation in the frequency of spike potentials in the sphincter of Oddi correlated to that of the migrating myoelectric complex in the duodenum, and therefore myoelectric activity of the sphincter of Oddi was also divided in phases I, II, III, and IV (Figure 2). The phases of the migrating myoelectric complex were determined by inspection of the recordings.

Usually there was no difference in the amplitude (4 to 10 mV) of sphincter of Oddi spike potentials in the same experiment, and 95% of the spike potentials originated in the proximal portion of the sphincter propagated distally. Some spike potentials had less amplitude and did not propagate from the proximal to the distal segment of the sphincter of Oddi. These action potentials were usually observed in phase I and at the beginning of phase II (Figure 3).

The frequency of sphincter of Oddi spike potentials was regular and increased gradually from phase I to reach the maximum frequency in phase III, then it decreased rapidly during phase IV to start a new myoelectric complex (Table

Figure 2. Myoelectric migrating complex phases (P) of the proximal (SO_1) and distal (SO_2) sphincter of Oddi and duodenum (D).

Figure 3. Electromyographic recording at the beginning of phase I shows spike potentials (arrows) originated in the proximal portion of the sphincter of Oddi (SO_1) that do not propagate distally (SO_2). These spikes have less amplitude. Duodenal tracing (D) can also be appreciated.

1). The sphincter of Oddi spike potentials never disappeared completely, even during phase I.

Table 1 also shows the average frequency of spike potentials of each phase in the duodenum and the duration of each migrating myoelectric complex phase. Since the number of slow waves and spike potentials were similar in the proximal and distal duodenum electrodes, only the distal electrode tracings were considered for analysis. This also pertains to the proximal and distal sphincter of Oddi electrodes, and only the distal sphincter of Oddi recordings were considered. The duration of each cycle was the same in the duodenum and sphincter of Oddi. All migrating myoelectric complex phases in the sphincter of Oddi started almost simultaneously with duodenal phases. The average duration of a migrating myoelectric complex cycle was 92 minutes. The amplitude of duodenal spike potentials was greater during phase III than during the other phases of the migrating myoelectric complex.

In the recordings of one opossum, influence of the duodenal myoelectric activity was observed on the sphincter of Oddi tracings. This electrical influence was simultaneous to the duodenal spike potentials and it was smaller (less than 2 mV) than the sphincter of Oddi spikes (Figure 4). Myoelectric influence of the sphincter of Oddi spike potentials on the duodenal tracings was also observed in the recordings of the same animal.

After feeding, the interdigestive phases of the

Table 1

Interdigestive Myoelectrical Activity of Sphincter
of Oddi and Duodenum

MMC Phase	Number of Spike Potentials* (spikes/min)		Duration* (min)
	SO	D	
I	3.0 ± 1.1	0	21.3 ± 4.2
II	4.7 ± 0.8	6.2 ± 2.3	56.3 ± 7.8
III	6.1 ± 0.4	15.1 ± 1.0	8.0 ± 0.9
IV	3.4 ± 0.9	6.3 ± 2.3	5.9 ± 0.7

Legend: SO, sphincter of Oddi; D, duodenum; MMC, myoelectric migrating complex.

*Values given as mean ± 1 SD

Figure 4. Recording A shows electrical influence (arrows) of the duodenal (D) spikes on the distal sphincter of Oddi (SO₂) tracing. These influences are not observed in the proximal part of the sphincter of Oddi (SO₁). Recording B depicts electrical influence (arrows) of the SO spikes on the D tracing.

migrating myoelectric complex in the sphincter of Oddi and duodenum were abolished and substituted by a feeding activity pattern (Figure 5). The feeding state was characterized by an average number of spike potentials in the sphincter of Oddi and duodenum of 6.6 ± 0.7 per minute (mean $\pm$ 1 SD) and 10.7 ± 1.6 per minute, respectively. The frequency of spikes in the sphincter of Oddi was more regular than in the duodenum. There was no change in the frequency of slow waves in the sphincter of Oddi and duodenum. The amplitude of sphincter of Oddi spike potentials was the same in the feeding and fasting states. After 2 to 3 hours the end of the feeding activity pattern was easily recognized by the reappearance of phase III.

Pressure studies.

The mean fasting pressure in the pancreatic and biliary ducts was 15 and 13 mmHg, respectively, and they ranged from 10 to 25 mmHg in the pancreatic duct and from 7 to 25 mmHg in the biliary duct. The pressure in the pancreatic duct was greater than the pressure in the biliary duct in 75% of the experiments, equal in 15%, and lower in 10%.

Pressure changes in the pancreatic and biliary ducts were of two types. First, there was a pressure oscillation of 1 to 3 mmHg synchronous with respiratory movements. This pressure variation could be eliminated from the recordings by turning the high-frequency cutoff filter knob to the mean position. The second type of pressure change was related to

Figure 5. Feeding activity pattern of the proximal (SO_1) and distal (SO_2) sphincter of Oddi and duodenum (D).

the sphincter of Oddi myoelectric activity. A temporary elevation of pancreatic and biliary duct pressures of 1 to 3 mmHg was observed with each sphincter of Oddi spike potential in most experiments (Figure 6). There was no pressure variation among the different migrating myoelectric complex phases.

There was an increase in the number of pressure elevations related to spike-burst potentials during feeding, but base pressure remained constant.

2.4. DISCUSSION

Several studies have been conducted to describe the dynamics and relationship of the pancreatic and biliary ducts to the sphincter of Oddi. Most methods of recording pancreatic and biliary duct pressures interfere with the flow of bile or pancreatic juice into the duodenum by occlusion of the ducts or interference with the normal sphincter activity (8,9). Recently, manometry during endoscopic cannulation of the papilla of Vater has been used extensively to measure the pancreatic and biliary ducts and sphincter of Oddi pressures (2,9). However, cannulation of the sphincter of Oddi can also interfere with its sphincteric activity or cause occlusion of the pancreatic or common duct.

Our model combines recording of sphincter of Oddi myoelectric activity with measurement of pancreatic and biliary duct pressures under circumstances that minimally

Figure 6. Recordings of the sphincter of Oddi (SO) myoelectric activity, common duct pressure (CD), and pancreatic duct pressure (PD). Temporary elevation of PD and CD pressures with each SO spike potential is seen. Oddi (SO)

disturb the normal pancreatobiliary physiology. The opossum was selected for this study because the sphincter of Oddi in this species is mostly extraduodenal and measures 2 to 3 cm in length and, therefore, is easily accessible. Placement of electrodes along the sphincter of Oddi may thus be accomplished without dissection of the pancreas and duodenum. In addition, the opossum provides another important advantage. These animals lie quietly during the day for many hours without the need of drug administration or use of restraints since they are nocturnal feeders.

The sphincter of Oddi in the opossum exhibited spontaneous spike potentials, which propagated from the proximal to the distal portion of the sphincter. Interestingly, the slow-wave frequency was the same in the sphincter of Oddi and duodenum, an average of 19 per minute. The number and amplitude of spike potentials in the sphincter of Oddi are different from those in the duodenum, but both the sphincter of Oddi and the duodenum exhibit cyclic changes in the frequency of spike potentials that correlate with the migrating myoelectric phases. The frequency of sphincter of Oddi and duodenal spike potentials increased from phase I to phase III of the migrating myoelectric complex and then it decreased rapidly during phase IV to start a new cycle. The average duration of each cycle was 92 minutes. The onset and duration of each phase were similar in the sphincter of Oddi and duodenum. During phase I occasional or no spike potentials were recorded on

the duodenum, while spikes were always present in the sphincter of Oddi.

Although the myoelectric activity of the sphincter of Oddi and duodenum is different, electrodes placed in the sphincter of Oddi close to the duodenum may record spike potentials generated in the duodenum and vice versa. This may be responsible for the electrical influence of the sphincter of Oddi spikes in the duodenum in the recordings of one of our animals. These electrical influences can be differentiated from true spike potentials because they are smaller than the spikes and are simultaneous to the action potentials that originated them. Electric currents propagate to any adjacent region in the small intestine as demonstrated by Specht and Bortoff (10).

The interdigestive migrating myoelectric complex cycles were disrupted by food. The feeding activity pattern was characterized by an increase in the number of spike potentials, both in the sphincter of Oddi and duodenum. De Wever et al. determined that the duration of the migrating myoelectric complex disruption is dependent on the quantity and nature of the food ingested (11). The disruptive effect is longer for fat than for carbohydrate. Protein abolished the migrating myoelectric complex for only short periods of time.

There is great controversy in the literature about the normal pancreatic and biliary pressures (1,2,8,9). The wide range of results is probably related to the numerous models,

techniques, and animals that have been used. In our study the recordings were performed in conscious opossums without the need for sedation, analgesics, or other drug-induced variables. The instruments used had high sensitivity and the electrodes and catheters probably did not disturb the pancreatobilioduodenal physiology. In preliminary studies we observed that infusion of large volumes of fluid into the pancreatic and biliary ducts disturbed the normal myoelectric activity of the sphincter of Oddi in some experiments. Therefore the rate of fluid administration was minimal.

The mean fasting pancreatic and biliary pressures were 15 and 13 mmHg, respectively. Temporary pressure elevations synchronous with each sphincter of Oddi spike potential were observed. The baseline pressure remained constant after feeding and during all migrating myoelectric complex phases.

The role of sphincter of Oddi spike potentials in the regulation of the pancreatic and biliary pressures is controversial. It has been suggested by combined electromyographic and cineradiographic studies that sphincter of Oddi spike potentials in opossums are associated with peristaltic contractions of the sphincter of Oddi that would have the function of transporting bile from the sphincter of Oddi into the duodenum (12,13,14). Simultaneously, the bile flow from the terminal common duct into the sphincter of Oddi would be interrupted temporarily with a secondary discrete increase in the biliary duct

pressure. After the sphincter of Oddi contraction, the sphincter segment would be refilled by passive inflow of bile from the common duct, and the baseline biliary pressure would be reestablished. A similar mechanism may also take place during pancreatic secretion. The constant baseline pancreatic and biliary duct pressures during all migrating myoelectric complex phases and feeding state suggest that pressure is not the main regulatory mechanism of bile and pancreatic juice flow into the duodenum. The purpose of different spike potentials during the various migrating myoelectric complex phases is unknown. We suggest that this spike potential variation may have an important role in regulating the rate of biliopancreatic secretion into the duodenum. Therefore biliary and pancreatic exocrine secretions would be more intense during phases II and III than during phases I and IV. This concurs with the study of Kaene et al. on dogs in which the trypsin and bicarbonate outputs were minimal during phase I and maximal during phase II and III, respectively. It is possible that the number of sphincter of Oddi spike potentials and the secretion of bile and pancreatic juice into the duodenum may be controlled simultaneously by a common mechanism, probably nervous or hormonal.

It is concluded that the sphincter of Oddi of the fasting opossum exhibits cyclic changes in the number of spike potentials that correlate with the migrating myoelectric complex in the duodenum. However, the number and

amplitude of spike potentials are different in the sphincter of Oddi and duodenum. Food ingestion disrupts the migrating myoelectric complex and increases the number of spike potentials in the sphincter of Oddi and duodenum. There was no change in the baseline pressure during fasting and feeding states, and a temporary pressure elevation synchronic with each sphincter of Oddi spike potential was observed.

2.5. SUMMARY

Myoelectric activity of the sphincter of Oddi and duodenum was correlated with pancreatic and biliary duct pressures in eight opossums, in both the fasted and fed states. Four bipolar electrode pairs were implanted in the sphincter of Oddi and duodenum. A polyethylene T tube was placed in the pancreatic duct. The common duct was cannulated through a small bile duct. This method allowed pressure recording for several weeks and avoided interference with the flow of bile or pancreatic juice into the duodenum. The frequency of slow waves was the same in the sphincter of Oddi and duodenum (19 per minute). The variation in the frequency of spike potentials in the sphincter of Oddi correlated to that of the migrating myoelectric complex in the duodenum. The average frequency of slow waves that have superimposed spike potentials in the sphincter of Oddi and duodenum was 3.0 and 0 in phase I, 4.7 and 6.2 in phase II, 6.1 and 15.5 in phase III, and 3.4 and

6.3 in phase IV, respectively. The average duration of a migrating myoelectric complex cycle was 92 minutes. After feeding, the interdigestive phases of the migrating myoelectric complex were abolished and substituted by a feeding pattern that was characterized by an average number of sphincter of Oddi and duodenum spikes of 6.6 and 10.7, respectively. The mean fasting pressure in the pancreatic and biliary duct was 15 and 13 mm Hg, respectively. Pressure changes were of two types: synchronous with respiratory movements and with each sphincter of Oddi spike potential. There was no variation in the baseline pressure during the migrating myoelectric complex phases and the fed state. It is concluded that the sphincter of Oddi of the fasting opossum exhibits cyclic changes in the number of spike potentials that correlate with the migrating myoelectric complex in the duodenum. However, the number and amplitude of spike potentials are different in the sphincter of Oddi and duodenum. There is no change in the baseline pressure during fasting and feeding states, and a temporary pressure elevation synchronic with each sphincter of Oddi spike potential was observed.

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CHAPTER 3

THE EFFECT OF FEEDING ON MYOELECTRIC ACTIVITY OF THE SPHINCTER OF ODDI AND GASTROINTESTINAL TRACT IN THE OPOSSUM

3.1. INTRODUCTION

Characteristic patterns of myoelectric activity occur in the gastrointestinal tract during fasting and after feeding in several species (1,2). The myoelectric migrating complex (MMC) is present during the fasting state and sweeps the gastrointestinal tract cyclically from the stomach to the terminal ileum. This pattern was first described by Szurszewski in 1969 and comprises four phases (3). During phase I, occasional or no spike potentials are observed. In phase II, spike potentials are superimposed on the slow waves in random fashion; phase III consists of spike potentials of high amplitude on each slow wave. During phase IV, the frequency and amplitude of spike potentials decrease rapidly to begin a new MMC. Feeding interrupts the MMC and results in a noncyclical pattern of intermittent spike potentials that persists for the duration of the postprandial period.

Recently, electromyography has been used to study the motility of the sphincter of Oddi (4,5). Honda et al. and our group have demonstrated that the sphincter of Oddi of the fasted opossum exhibited cyclic changes in the frequency of bursts of spike potentials that correlated with the MMC

phases (6,7). Feeding abolished the MMC phases in the sphincter of Oddi. The fed pattern of the small bowel has been reported in several studies (8,9,10). However, the effect of different foods on the myoelectric activity of the antrum and sphincter of Oddi has not been evaluated. A relationship between flow of biliary and pancreatic secretions into the duodenum and the MMC phases has also been reported (11). Our objective in the present study is to determine the effect of different foods on the myoelectric activity of the sphincter of Oddi and correlate it with the fed pattern of the gastrointestinal tract in the opossum. Simultaneous gallbladder pressure recordings were also obtained.

3.2. MATERIAL AND METHODS

The opossum was selected for this study because its sphincter of Oddi is mainly extraduodenal and measures 2 to 3 cm in length and, therefore, dissection of the pancreas and duodenum is not necessary to implant the electrodes. In addition, in the opossum, as in the human, the main pancreatic duct joins the common duct at the proximal portion of the sphincter of Oddi.

Laparotomy was performed in five opossums of either sex weighing 2.5 to 3.5 kg. The animals were anesthetized with 25 mg of sodium pentobarbital per kg administered intraperitoneally.

A total of 14 bipolar electrodes were implanted as

pairs into the sphincter of Oddi, distal gastric antrum, duodenum, proximal jejunum, mid-jejunum, terminal jejunum, and terminal ileum. The electrodes consisted of stranded silver-plated copper wire of 36 AWG (American Wire Gauge) size with teflon insulation. The wire was placed in the muscular layer of the gastrointestinal tract through a 25 gauge hypodermic needle and the end was tied off. The free end was trimmed.

A large silastic tube (1/16 inch I.D. and 1/8 inch O.D.) was placed into the stomach, 2 cm distal to the esphagogastric junction. A cholecystostomy was performed with PE-50 polyethylene tubing in the fundus of the gallbladder in four animals. The tubes and the wires were passed through a subcutaneous tunnel to the back of the animal.

An eight-channel Gould 2800S instrument (Gould Inc., Recording Systems Division, Cleveland, Ohio) was employed to record the electromyographic activities and the gallbladder pressure. Experiments were begun seven to ten days after the operation and were performed on conscious animals fasted for 12 hours.

Pressure was recorded by connecting the gallbladder catheter to the recording instrument through a Gould P23 pressure transducer (Gould Statham Instruments, Inc., Hato Rey, Puerto Rico). An Arndorfer hydraulic capillary infusion system (Arndorfer Medical Specialties, Inc., Greendale, Wisconsin) was employed to infuse water into the catheter at

a low constant rate of 0.04 ml/min. In order to eliminate the pressure secondary to the tubing resistance to the water flow, another catheter with the same diameter as that placed in the gallbladder was perfused with water at the same rate. The pressure recorded from the external catheter was considered to be zero.

Four types of food were studied: 90% protein (Milk and Egg Protein, Fillmore Foods, Inc., Suisun, California), pure fat (Corn Oil, Sigma Chemical Co., St. Louis, Missouri), pure carbohydrates (C & C Sugar, California and Hawaiian Sugar Co., San Francisco, California), and mixed food that contained the same amount of calories in fat, protein, and carbohydrates.

Because caloric content was the only common property of the meals, the quantity of food used was expressed in calories as suggested by De Wever et al. (6). Each meal, at 20 Cal/kg, was given through the gastrostomy tube to make certain that the food was completely ingested. The food was mixed with water to obtain meals with a constant volume of 50 ml.

Ten studies were obtained for each type of food. Each study included recordings of one MMC preceding instillation of food, the fed pattern, and one MMC following the meal. The meal was given during phase I of the MMC.

The duration of the fed pattern was determined by measuring the interval between feeding and the reappearance of the first phase III in the duodenum that migrated

distally to the ileum, and it was followed by phase I. The frequency of bursts of spike potentials in the sphincter of Oddi, antrum, duodenum, and mid-jejunum was determined by dividing the recordings into two-minute intervals and averaging the number of slow waves with spikes in each interval during the entire fasted and fed states. The MMC was divided into four phases as described by Code and Marlett (12). The data were analyzed statistically by means of analysis of variance. Correlation between frequency of spike potentials in the sphincter of Oddi and small bowel and the duration of the fed pattern was determined by linear correlation analysis.

3.3. RESULTS

Fasting Myoelectric Activity

The frequency of slow waves (presetter potential) was the same in the sphincter of Oddi and duodenum, and decreased from 19/min in the duodenum to 16/min in the ileum. The presetter potential frequency in the antrum was the lowest, 3.5/min. The frequency of slow waves with spike potentials in the sphincter of Oddi and gastrointestinal tract for each MMC phase is shown in Table 1. Bursts of spike potentials never disappeared completely in the sphincter of Oddi, even though no spike potentials were observed in the stomach and small bowel during phase I. Phase III in the small bowel was characterized by spike potentials on each slow wave. However, spike potentials were

observed in only 78% and 23% of the slow waves in the antrum and sphincter of Oddi, respectively, during phase III (Figure 1). The average duration of the MMC was 81 min with phase II being the longest (Table 1).

Fed Myoelectric Activity

Feeding caused appearance of spike activity in the duodenum and sphincter of Oddi in five minutes and in the jejunum in ten minutes. All meals caused an increase of slow waves with spikes in the duodenum (9.5 spike bursts/min) and sphincter of Oddi (7 spike bursts/min) during the first two minutes as compared to the frequency of bursts of spikes observed during the 15 minute interval preceding the feeding. This burst of spike potentials was followed by a pattern of irregular spike activity. This fed pattern was the longest for fat and the shortest for carbohydrates ($p < 0.01$) (Table 2).

The average number of slow waves with superimposed spike potentials following feeding of each type of food is also shown in Table 2. Feeding of fat and mixed food resulted in the greatest incidence of spike activity in the duodenum and jejunum, followed by protein. The lowest incidence of slow waves with spikes in the duodenum and jejunum followed feeding of carbohydrates ($p < 0.01$). There were no differences between fat and mixed food except for spike activity in the jejunum, which was higher for fat ($p < 0.01$). There was a correlation between the frequency of

Figure 1. Myoelectric migrating complex phases (P) of the gastric antrum (A), duodenum (D), and sphincter of Oddi (SO) in the fasted opossum. The phases observed in the jejunum and ileum were similar to those recorded from the duodenum except for the frequency of the slow waves, which were slightly lower in the jejunum and ileum.

TABLE 1

Myoelectric Activity of the Sphincter of Oddi
and Gastrointestinal Tract During Fasting

Spike Activity Frequency (spike bursts/min) (n = 40)	Myoelectric Migrating Complex Phases			
	I	II	III	IV
Sphincter of Oddi	1.1 $\pm$ 0.4	3.4 $\pm$ 0.7	4.3 $\pm$ 0.6	3.2 $\pm$ 0.7
Antrum	0	2.3 $\pm$ 0.3	2.7 $\pm$ 0.3	2.1 $\pm$ 0.4
Duodenum	0	3.5 $\pm$ 0.8	17.8 $\pm$ 0.6	4.9 $\pm$ 1.5
Jejunum	0	6.1 $\pm$ 0.9	17.1 $\pm$ 0.7	5.0 $\pm$ 1.7
*Duration (min)	27.7 $\pm$ 3.9	39.3 $\pm$ 5.9	8.0 $\pm$ 0.4	5.8 $\pm$ 0.7

*Duration of each phase in the duodenum
n refers to the number of experiments

TABLE 2

Myoelectric Activity of the Sphincter of Oddi, Duodenum
and Jejunum After Feeding

Spike Activity Frequency (spike bursts/min) (n = 10)	Fat	Protein	Carbohydrates	Mixed Food
Sphincter of Oddi	4.3±0.8	3.7±1.1*	2.8±0.6	4.2±1.0
Antrum	< 0.5	< 0.5	< 0.5	< 0.5
Duodenum	6.9±0.9	6.3±1.5**	3.1±0.8	7.3±1.7
Jejunum	10.6±1.1**	7.7±1.2**	5.6±0.7	8.6±1.4
Duration (min)	218±47**	165±26**	131±26	197±61

*Indicates that this value is significantly greater than the corresponding value in the next column to the right at the 5 percent level, $p < 0.05$.

**Indicates that this value is significantly greater than the corresponding value in the next column to the right at the 1 percent level, $p < 0.01$.

n refers to the number of experiments.

bursts of spike potentials in the small bowel and sphincter of Oddi and the duration of the fed pattern (correlation coefficient = 0.605; $p < 0.01$).

Only spike potentials of low amplitude were observed in the antrum following all types of meals (Figure 2). Although these spike potentials occurred during the entire fed state, they were more frequent immediately after feeding and in the 10 minute period preceding the reappearance of phase III.

The lowest incidence of spike potentials in the sphincter of Oddi was observed after feeding carbohydrate ($p < 0.05$). There was no significant difference in frequency of spike potentials in the sphincter of Oddi between fat, protein, and mixed food. There was a correlation between the frequency of bursts of spike potentials in the sphincter of Oddi and duodenum (correlation coefficient = 0.538. $p < 0.01$) and sphincter of Oddi and jejunum (correlation coefficient = 0.339; $p < 0.05$).

Gallbladder Pressure

There was no significant change in gallbladder pressure during fasting and following feeding of different aliments. The mean gallbladder pressure during fasting was 8.7 ± 1.5 mmHg and ranged from 7 to 12 mmHg. The mean pressures after feeding were 10.3 ± 2.1 for fat; 9.7 ± 1.9 for carbohydrates, and 9.5 ± 1.6 for mixed food.

Figure 2. Electromyographic recordings of the gastric antrum obtained from the same animal in one experiment. Recording A shows slow waves with spike potentials of large amplitude observed during phase II of the myoelectric complex. Recording B depicts slow waves with spikes of low amplitude seen during the fed pattern.

3.4. DISCUSSION

The myoelectric activity of the small bowel after feeding has been studied previously in other species (13,14, 15). Ruckebusch et al. determined in pigs that the duration of disruption of the MMC after feeding depended on the volume of the meal (16). De Wever et al. observed a linear relation between the amount of calories of the test meal and the duration of disruption of the MMC in dogs (10).

In the present study, we have evaluated the effect of isocaloric amounts of pure and mixed nutrients on the myoelectric activity of the sphincter of Oddi and gastrointestinal tract. A correlation between the frequency of spike potentials in the sphincter of Oddi and the small bowel was observed. The nutrients that caused more spike potentials in the duodenum and jejunum were also the ones that increased more spike activity in the sphincter of Oddi. The duration of the fed pattern correlated with the frequency of bursts of spike potentials in the sphincter of Oddi and gastrointestinal tract. Fat and protein caused the greatest frequency of spike activity in the sphincter of Oddi and small bowel, and the longest fed pattern. The spike activity of the sphincter of Oddi and small bowel after feeding carbohydrate was the lowest.

The low frequency of spike activity in the antrum observed after feeding was probably related to the consistency of the food employed. In contrast to its major role in gastric emptying of solids, the antrum has a less

essential role in the propulsion of liquids. Although antral contractions most likely aid propulsion of liquid from the stomach regardless of the presence or absence of such contractions (17).

Gastric emptying of carbohydrates is generally faster than proteins, which empty faster than fats (18). However, when isocaloric amounts of nutrients are employed, fat, protein, and carbohydrates empty at similar rates (19). Therefore, gastric emptying possibly did not play a role in the duration of the fed pattern or in the intensity of the spike activity of the small intestine in the present experiment.

Recently, gallbladder pressure has been correlated with MMC phases in the duodenum. Itoh and Takahashi observed that gallbladder pressure in the dog increases when duodenal phase II of the MMC starts and decreases toward phase II (20). Traynor et al. reported a brief elevation of gallbladder pressure in the dog for two minutes at the beginning of phase I (21). The pressure during phase III was constant and similar to phase I of the MMC. We have not observed pressure changes during the MMC phases and the increase in gallbladder pressure following feeding was not statistically significant. These differences may be related to the species employed. Dubois and Hunt reported differences in gallbladder contraction between different species (22). The gallbladder of the opossum usually evacuated less than one-third of its contents after a fat

meal, while the gallbladder of the cat emptied all its contents under the same conditions. They suggest that this difference may be related to the larger volume and thinner muscular layer of the gallbladder of the opossum as compared to the gallbladder of the cat. However, the transit time of bile in the biliary ducts was the same in the two species. Therefore, only smaller changes in gallbladder pressure may be necessary for evacuation of the same volume of bile in the opossum. These small increases in pressure may be difficult to detect due to the wide range of resting gallbladder pressure.

We conclude from this study that fat and mixed food caused the highest spike activity in the duodenum and jejunum, followed by protein. There was no difference in frequency of sphincter of Oddi spike potentials between fat, mixed food, and protein. Carbohydrates caused the lowest incidence of spike activity in the sphincter of Oddi and small bowel.

3.5. SUMMARY

The effect of different foods on the myoelectric activity of the sphincter of Oddi and gastrointestinal tract was evaluated in the opossum. Gallbladder pressure was also recorded. Feeding fat and mixed food resulted in the greatest incidence of spike activity in the duodenum and jejunum, followed by protein. The lowest incidence of slow waves with spikes in the duodenum and jejunum followed

feeding of carbohydrates ($p < 0.01$). Likewise, the lowest spike activity in the sphincter of Oddi was observed after carbohydrate ($p < 0.05$). There was no significant difference in the incidence of spike potentials in the sphincter of Oddi when fat, protein, or mixed food was fed. No significant change in gallbladder pressure during fasting and following feeding of different aliments was observed. We concluded that there is a correlation between the frequency of spike potentials in the sphincter of Oddi and in the small bowel following feeding. The duration of the fed pattern for each type of food correlated with the number of spikes in the sphincter of Oddi and gastrointestinal tract.

3.6. REFERENCES

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CHAPTER 4

EFFECT OF GASTROINTESTINAL HORMONES ON THE SPHINCTER OF ODDI AND DUODENUM MYOELECTRIC ACTIVITY AND ON PANCREATIC AND BILIARY PRESSURES IN THE OPOSSUM

4.1. INTRODUCTION

Although disturbances of the sphincter of Oddi have been implicated in the pathogenesis of biliary and pancreatic diseases, little is known about its normal sphincteric physiology. Manometric, flowmetric, cineradiographic, and endoscopic techniques have been employed to evaluate the dynamics of the sphincter of Oddi (1-4). Recently, electromyography has been used to study the motility of the gastrointestinal tract and its sphincters (5-8). Several animals, including man, opossum, and dog, exhibit a characteristic gut motility during the fasting state that has been termed the migrating myoelectric complex (MMC) which periodically propagates down the digestive tract from the stomach to the terminal ileum (5,6). Following

feeding, the MMC cycle is temporarily substituted by a myoelectric fed pattern. Honda et al. and our group have demonstrated that the sphincter of Oddi of a fasting opossum exhibits cyclic changes in the frequency of spike potentials that correlate with the MMC in the duodenum (5,6).

Correlation between myographic activity of the sphincter of Oddi and pancreatic and biliary duct pressures has not yet been evaluated. We have developed a chronic model that allows simultaneous recording of the sphincter of Oddi electromyography and measurement of pancreatic and biliary pressures. Our objective in the present study is to evaluate the effect of gastrointestinal hormones and acetylcholine on the sphincter of Oddi and duodenum myoelectric activity and on pancreatic duct and common duct pressures in the awake, nonmedicated opossum.

4.2. MATERIAL AND METHODS

Experiments were performed in eight adult opossums of either sex weighing 3 to 5 kg. The animals were anesthetized with 25 mg of sodium pentobarbital per kg administered intraperitoneally.

At laparotomy, performed through an upper midline incision, the main pancreatic duct at the head of the pancreas was catheterized with a PE-50 polyethylene T-tube

(Figure 1). The bile duct, which connects the right lateral lobule of the liver to the common duct, was cannulated with a PE-50 polyethylene tube.

Four pairs of bipolar extracellular electrodes were implanted in the sphincter of Oddi and duodenum, two in each site. In the sphincter of Oddi, which measures 2 to 3 cm in length in the opossum, the electrode pairs were placed 1 cm and 2 cm proximal to the sphincter of Oddi-duodenal junction. The third and fourth pairs of electrodes were fixed in the duodenum 2 cm proximal and 2 cm distal to the sphincter of Oddi-duodenal junction. The electrodes consisted of stranded silver-plated copper wire with teflon insulation of 36 AWG size.

The biliary and pancreatic catheters and the wires were previously passed through a subcutaneous tunnel from the back to the right upper quadrant of the abdomen. The wires were soldered to a female connector prior to the operation. After abdominal wall closing, a silastic tube was inserted into the internal jugular vein. The tube was passed to the animal's back where it exited. The socket and the tubes were stitched to the skin.

Electromyographic activities and biliary and pancreatic duct pressures were simultaneously recorded on an eight-channel Gould 2800S instrument (Gould Inc., Recording Systems Division, Cleveland, Ohio). Experiments were begun seven to ten days after the operation and were performed on conscious fasted animals. Recording sessions of five to

Figure 1. Cholangiopancreatogram showing the common duct (CD) and a T-tube placed in the main pancreatic duct (p).

eight hours were obtained in each animal for a period of one to four months with an average of eight recording sessions per opossum.

The following substances and doses were studied: 0.02, 0.1 and 0.5 $\mu\text{g/kg/h}$ of cholecystokinin-octapeptide (E.R. Squibb & Sons, Inc., Princeton, New Jersey); 1, 2 and 4 $\mu\text{g/kg/h}$ of pentagastrin (Ayerst Laboratories, New York, New York); 1, 2 and 10 $\mu\text{g/kg/h}$ of glucagon (Eli Lilly, Indianapolis, Indiana); 1, 2 and 10 $\mu\text{g/kg/h}$ of secretin (Squibb & Sons, New York, New York); and 50, 100 and 200 $\mu\text{g/kg/h}$ of acetylcholine (Merck Co. Inc., Rahway, New Jersey). Six observations were obtained for each substance and dose. The substances were infused intravenously at a rate of 0.1 ml/min employing a Harvard pump. The infusion started at the beginning of phase I of the MMC and lasted for one MMC or, in the case of MMC interruption, for one to two hours. Acetylcholine was usually administered for only 15 minutes due to intense collateral effects observed in the animals, namely dyspnea, sialorrhea, and agitation. One normal MMC was recorded as control preceding the infusions. Each substance was administered two or three times in each animal with an interval of at least three days between the infusions.

For each recording session, a male socket connected through isolation preamplifiers to the recording system was plugged into the animal back socket. Electromyographic recordings were performed using a paper speed of 1 mm/s, low

frequency cut-off filter of 1 Hz, high frequency cut-off filter of 10 Hz, and overall sensitivity of 100 mV.

Pressures were registered by connecting the pancreatic and biliary catheters to the recording instrument through Gould P23 pressure transducers (Gould Statham Instruments, Inc., Hato Rey, Puerto Rico). The catheters were infused with water at a constant rate of 0.04 ml/min employing an Arndorfer hydraulic capillary infusion system (Arndorfer Medical Specialties, Inc., Greendale, Wisconsin). The Arndorfer infusion system measures pressure resistance to a constant fluid infusion rate delivered through stainless steel capillaries. In order to eliminate the pressure secondary to water flow into the tubes, catheters equal to those placed in the pancreatic and biliary ducts were perfused with water at a flow rate of 0.04 ml/min. The tip of each external catheter was placed at the same height as the internal catheter while the opossum was lying on its abdomen. The pressure recorded from the external catheters was considered to be zero level.

Although reduction of the flow rate decreases the sensitivity of the pressure recording system, we have selected a smaller infusion rate (0.04 ml/min) than the recommended (0.25 ml/min) by the manufacturer of the Arndorfer infusion system to study biliary pressure. We have observed in preliminary experiments that fluid infusion at 0.25 ml/min into the small pancreatic and biliary ducts of the opossum increased the motility of the sphincter of Oddi and

artificially elevated the biliary and pancreatic pressures. The sensitivity of the pressure recording system was tested by elevating the tip of the external catheters 10 cm. This caused an increase in pressure of 7.5 mmHg. The time constant at flow rate of 0.04 ml/min was 1.68 sec and at 0.25 ml/min was 1.2 sec. The time constant was defined as the time in seconds for the pressure to rise to approximately two-thirds of 10 mmHg.

MMC activity in the duodenum was divided into four phases according to the method described by Code and Marlett (9). Since changes in the sphincter of Oddi frequency of spike potentials correlate with the MMC cycle in the duodenum, the myoelectric activity of the sphincter of Oddi was also divided into four phases. Inspection of the recordings revealed that the number of slow waves and spike potentials was similar in the proximal and distal duodenum electrodes and in the proximal and distal sphincter of Oddi electrodes; therefore, only recordings of the distal duodenum and sphincter of Oddi electrodes were considered for analysis. The recordings were divided into two-minute intervals and the average frequency of slow waves with superimposed spike potentials for each phase of the MMC was determined. In instances of MMC interruption, the average frequency of spike potentials was calculated from 15 min to 60 min after the onset of hormone infusion. The data were analyzed statistically by means of the student two-tailed test. Determination of dose dependency was made by linear

regression analysis. The average frequency of spike potentials for each experiment was plotted against the logarithmic hormone concentration. In the text, averaged values are given as mean $\pm$ 1SD.

4.3. RESULTS

Control Fasting Myoelectric Pattern

Although the frequency of spike potentials was different in the sphincter of Oddi and duodenum, both frequencies increased gradually from phase I to reach the maximum frequency in phase III, then they decreased rapidly during phase IV to start a new MMC. The variation in the frequency of spike potentials in the sphincter of Oddi correlated with the MMC phases in the proximal duodenum and, therefore, myoelectric activity of the sphincter of Oddi was also divided in phases I, II, III and IV (Figure 2). All phases in the sphincter of Oddi started almost simultaneously with the MMC phases in the proximal duodenum.

The average frequency of spike potentials in the sphincter of Oddi and duodenum for each MMC phase and the duration of each phase in the duodenum are shown in Table 1. The frequency of slow waves was the same in the sphincter of Oddi and duodenum, and averaged 18/min.

Figure 2. Myoelectric migrating complex phases (P) of the duodenum (D) and sphincter of Oddi (SO).

TABLE 1

Normal Myoelectric Migrating Complex (MMC)
Of the Sphincter of Oddi (SO) and Duodenum (D)

MMC Phase	Frequency of Spike Potentials (spikes/min)		Duration in the Duodenum (min)
	SO	D	
I	2.9 ± 1.0	0	28.0 ± 5.1
II	4.7 ± 1.1	6.4 ± 2.0	48.8 ± 6.9
III	5.9 ± 0.4	15.3 ± 1.0	8.0 ± 0.9
IV	3.2 ± 0.6	5.7 ± 1.8	5.5 ± 0.8

Effect of Cholecystokinin and Pentagastrin on Myoelectric Activity

Within eight minutes after the beginning of cholecystokinin or pentagastrin infusion, sphincter of Oddi and duodenum spike potential frequency started to increase in all experiments. Interruption of the MMC was observed in 12 (67%) experiments with cholecystokinin and 16 (89%) with pentagastrin. The new myoelectric activity pattern resembled that of a fed state with average spike potential frequencies that varied from 6.4 ± 0.7 to 7.7 ± 1.1 in the sphincter of Oddi and from 5.5 ± 0.9 to 7.9 ± 0.8 in the duodenum (Table 2). These values were all significantly higher than the control values of 2.9 ± 1.0 in the sphincter of Oddi and 4.1 ± 1.2 in the duodenum, obtained by averaging the frequency of spike potentials during phases I and II of the normal MMCs ($p < 0.01$). The change in spike activity was dose-dependent both in the sphincter of Oddi and duodenum ($p < 0.01$). Although there was an increase in the number of sphincter of Oddi and duodenum spike potentials during phase II, no MMC interruption was observed in six instances (33%) of cholecystokinin infusion (4 experiments - $0.02 \mu\text{g/kg/h}$ and 2 experiments - $0.1 \mu\text{g/kg/h}$) and in two instances of pentagastrin administration ($1 \mu\text{g/kg/h}$ each).

Effect of Glucagon and Secretin on Myoelectric Activity

Glucagon and secretin inhibited the onset of MMC for at least one hour in four (22%) and ten (56%) experiments

TABLE 2

Myoelectric Activity of the Sphincter of Oddi and Duodenum
Following Cholecystokinin and Pentagastrin Infusion

Frequency of Spike Potentials (spikes/min)	Sphincter of Oddi	Duodenum
<u>cholecystokinin*</u>		
0.02 $\mu\text{g/kg/h}$	6.4 ± 0.7	6.1 ± 0.9
0.1 $\mu\text{g/kg/h}$	7.4 ± 0.8	7.2 ± 1.0
0.5 $\mu\text{g/kg/h}$	7.7 ± 1.1	7.9 ± 0.8
<u>pentagastrin*</u>		
1 $\mu\text{g/kg/h}$	6.3 ± 0.6	5.5 ± 0.9
2 $\mu\text{g/kg/h}$	7.0 ± 1.0	7.0 ± 0.6
4 $\mu\text{g/kg/h}$	7.7 ± 0.9	7.8 ± 0.6

*The correlation coefficient for cholecystokinin in the sphincter of Oddi and duodenum was 0.789 and 0.790 respectively ($p < 0.01$). The coefficients for pentagastrin were 0.653 and 0.822 respectively ($p < 0.01$).

respectively, in which occasional or no spike potentials were observed in the sphincter of Oddi and duodenum during the entire infusion period. In these instances, glucagon was infused at 10 $\mu\text{g/kg/h}$ in all four experiments and secretin at 10 $\mu\text{g/kg/h}$ in six experiments, at 2 $\mu\text{g/kg/h}$ in three experiments, and at 1 $\mu\text{g/kg/h}$ in one experiment. This sphincter of Oddi electromyographic pattern differs from the normal MMC in which spike potentials were always observed in the sphincter of Oddi. In the remaining instances, infusion of glucagon and secretin reduced the total percentage of slow waves with superimposed spike potentials in the sphincter of Oddi and duodenum. The average number of spike potentials in the sphincter of Oddi and duodenum for each MMC phase after administration of glucagon and secretin is shown in Table 3. For this analysis, the responses to the three doses of glucagon and secretin were averaged. When compared to the MMC preceding glucagon and secretin infusion, this reduction of spike potentials was statistically significant during phases I and II in the sphincter of Oddi and during phases II and IV in the duodenum ($p < 0.01$).

Effect of Acetylcholine on Myoelectric Activity

Acetylcholine increased the number of spike potentials in the sphincter of Oddi and in the duodenum. For this analysis, the average frequency of slow waves with superimposed spike potentials was determined from 2 min to

TABLE 3

Myoelectric Migrating Complex (MMC) Of Sphincter of Oddi (SO)
and Duodenum (D) Following Glucagon and Secretin Infusion[†]

MMC Phase	Frequency of Spike Potentials (spikes/min)					
	Glucagon		Secretin		Control	
	SO	D	SO	D	SO	D
I	1.6±0.8*	0	1.6±0.4*	0	2.9±1.0	0
II	3.2±0.8*	4.8±1.4*	2.8±0.5*	2.1±0.8	4.8±0.7	6.3±1.2
III	5.6±0.4	14.8±0.8	5.4±0.5	14.8±0.6	5.6±0.8	15.2±0.4
IV	2.9±0.4	4.1±0.6*	3.0±0.4	4.5±0.8	2.8±0.8	5.8±0.8

[†]Four experiments of glucagon infusion and ten experiments of secretin infusion in which the MMC was inhibited were not included in this analysis. In these instances, the frequency of spike potentials in the sphincter of Oddi and duodenum was 0.

*Indicates that this value is significantly smaller than the corresponding control value at the 1 percent level, $p < 0.01$.

15 min after the onset of acetylcholine infusion. The largest increase in spike potential frequency was observed with infusion of 200 $\mu\text{g/kg/h}$; at this dose, almost each slow wave was superimposed with spike potentials in the sphincter of Oddi (17 ± 0.1) and duodenum (18 ± 0.1). Average spike potential frequencies following infusion of 50 and 100 $\mu\text{g/kg/h}$ of acetylcholine were 11 ± 0.2 and 14 ± 0.1 spikes/min in the sphincter of Oddi and 13 ± 0.2 and 16 ± 0.1 spikes/min in the duodenum respectively. The increase in frequency of spike potentials in the sphincter of Oddi and duodenum was dose-dependent and the correlation coefficients were 0.882 and 0.869 respectively.

Biliary and Pancreatic Pressure Studies

The mean control pressures in the common and pancreatic ducts were 14 ± 2.5 and 15 ± 2.6 mmHg respectively and they ranged from 7 to 17 mmHg in the common duct and from 8 to 19 mmHg in the pancreatic duct. Temporary elevations of the biliary and pancreatic pressures of 1-3 mmHg were seen simultaneously with each spike potential in the sphincter of Oddi and with the respiratory movements. There was no baseline pressure variation among the different MMC phases.

Although there was variation in the frequency of pressure elevations related to sphincter of Oddi spike potentials, the baseline pressures remained constant during infusion of the hormones (Figure 3). The mean biliary and

Figure 3. Recordings of the sphincter of Oddi (SO) myoelectric activity, common duct pressure (CD), and pancreatic duct pressure (PD) before (A) and 15 min after the beginning of pentagastrin infusion at $2 \mu\text{g/kg/h}$ (B). Pentagastrin increased the spike potential frequency in the sphincter of Oddi and the frequency of biliary and pancreatic pressure oscillations related to sphincter of Oddi spike potentials, but the base-line pressures remained constant.

pancreatic pressures were respectively 13.7 ± 2.1 and 14.2 ± 1.7 for cholecystokinin; 13.4 ± 1.4 and 14.3 ± 2.7 for pentagastrin; 13.2 ± 1.9 and 14.7 ± 1.6 for glucagon and 14.0 ± 2.3 and 15.3 ± 2.2 for secretin. Acetylcholine infusion increased the mean biliary and pancreatic pressures to 29.0 ± 4.6 and 31.0 ± 5.6 respectively ($p < 0.01$) (Figure 4).

4.4. DISCUSSION

Recent advances in electromyographic techniques allowed a more direct evaluation of the sphincter of Oddi function. It has been demonstrated that the sphincter of Oddi in the opossum exhibits spontaneous spike potentials which propagate from the proximal to the distal portion of the sphincter (5). Although the number and intensity of spike potentials in the sphincter of Oddi are different from those in the duodenum, both the sphincter of Oddi and duodenum exhibit cyclic changes in the frequency of spike potential that correlate with the phases of the MMC. Both frequencies increase gradually from phase I to phase III then they decrease rapidly during phase IV to start a new MMC.

Several studies, including this one, have demonstrated that cholecystokinin and pentagastrin increase the spike burst frequency of the sphincter of Oddi and duodenum and,

Figure 4. Recordings showing the effect of acetylcholine infusion (arrow) at $200 \mu\text{g/kg/h}$ on the sphincter of Oddi (SO) myoelectric activity, common duct pressure (CD) and pancreatic duct pressure (PD). Temporary elevation of CD and PD pressures with each SO spike potential is seen before acetylcholine administration. Intense SO spike activity and continuous elevation of CD and PD during acetylcholine infusion is also shown.

in most instances, these hormones disrupt the MMC (10,11). The new myoelectric pattern resembles that of the fed state.

Few studies have evaluated the effect of glucagon on the myoelectric activity of the gastrointestinal tract. Honda et al. have described recently that glucagon infusion decreased the spike burst frequency of the sphincter of Oddi and may abolish the appearance of MMC activity of the gastrointestinal tract of the opossum (10). Geenen et al. observed a reduction in sphincter of Oddi pressure activity on intraluminal pressure recording of human sphincter of Oddi (12). Our study also demonstrated that glucagon infusion depressed significantly the frequency of sphincter of Oddi and duodenum spike potentials.

The effect of secretin on the myoelectric activity of the sphincter of Oddi is controversial. Becker et al. observed no significant effect on sphincter of Oddi motor activity of the opossum (7). Geenen et al. described that secretin caused a mixed response of excitation followed by inhibition of the sphincter of Oddi motor activity of the human (12). We have observed that secretin consistently decreased the sphincter of Oddi and duodenum spike burst frequencies and that in most instances it delayed the onset of the MMC. Our findings concur with the studies of Mukhopadhyay et al. (13) and Wingate et al. (14) on the effect of secretin on the myoelectric activity of the small intestine of the dog. Mukhopadhyay et al. demonstrated that secretin blocked the initiation of the myoelectric complex

in the small bowel and Wingate et al. showed that the spike activity of the duodenum and jejunum was decreased during infusion of secretin.

The doses of the substances administered in this study were the same employed in other works to evaluate the motility of the gut (7,10-14). The physiologic doses of hormones have been difficult to determine since the hormonal levels vary widely with the animal species, the method used, and with the prandial state of the animal.

In order to measure the pancreatic and biliary duct pressures, we have developed a model which minimally disturbs the pancreatobilioduodenal physiology. This model allowed pressure recordings for several weeks in conscious animals without the need of anesthesia or drugs.

Toouli et al., using combined electromyographic and cineradiographic techniques in the opossum, have observed two mechanisms of fluid transport from the common bile duct into the duodenum (15,16). First, spike potentials in the sphincter of Oddi were associated with peristaltic contractions of the sphincter and milking of contrast fluid into the duodenum. This concurs with our observation that spike activity of the sphincter of Oddi increases during fluid infusion into the common bile duct. In addition, this might also explain the paradoxical effect of cholecystokinin on the sphincter of Oddi of opossum. Infusion of cholecystokinin stimulates the sphincter of Oddi spike potential, possibly allowing the transport of excess bile

originating from the gallbladder into the duodenum. A second mechanism was observed during administration of histamine and amyl nitrate, substances known to cause inhibition of sphincter of Oddi spike activity (17). These drugs abolished sphincter of Oddi contractions and caused the entire sphincter of Oddi to remain open while contrast medium flowed passively into the duodenum. Secretin causes a sphincter of Oddi myoelectric activity pattern similar to that of histamine and, therefore, secretin possibly may also increase the flow of fluid into the duodenum by relaxing the entire sphincter segment.

Toouli et al. have demonstrated in the opossum that the bile flow from the terminal common duct into the sphincter of Oddi would be interrupted temporarily at the moment the peristaltic contraction reaches the proximal portion of the sphincter of Oddi (17). This would cause a temporary increase in the common duct pressure with each sphincter of Oddi spike potential, which we have recorded in our study. Following the sphincter of Oddi contraction, the sphincter segment would be refilled by a passive inflow of bile from the common duct and the baseline biliary pressure would be re-established. Intense sphincter of Oddi spike activity, as observed during acetylcholine infusion, would hamper bile refilling of the sphincter of Oddi and therefore would elevate the bile duct pressure. This would be analogous to cardiac fibrillation. A similar mechanism may also take place during pancreatic secretion.

Variation of the number of pancreatic and biliary duct pressure oscillations related to change in spike potential frequency was observed during hormone infusions, but the baseline pressure remained constant. On the contrary, Becker et al. observed that the common duct pressure increased during administration of cholecystokinin in the opossum (7). The conflicting results may be related to the higher infusion rate of fluid into the common bile duct employed by Becker et al. Our findings suggest that the pancreatic and biliary duct pressures are maintained at a constant level by increasing or decreasing the flow of bile or pancreatic juice into the duodenum through changes in the frequency of sphincter of Oddi spike potential. It is possible that the substances that increase the secretion of bile and pancreatic juice in the opossum would also simultaneously change the frequency of sphincter of Oddi spike potentials and therefore maintain constant duct pressures.

We conclude that cholecystokinin and pentagastrin stimulates the spike potential frequency of the sphincter of Oddi and may change the myoelectric activity to a fed-like pattern. Glucagon and secretin decrease the burst spike activity and may inhibit the onset of the MMC. These hormones may have an important role in regulating the excretion of bile and pancreatic juice into the duodenum.

4.5. SUMMARY

Myoelectric activity of the sphincter of Oddi and duodenum was correlated with common duct and pancreatic duct pressures in conscious opossums after infusion of the following substances: cholecystokinin, pentagastrin, glucagon, secretin, and acetylcholine. Cholecystokinin and pentagastrin increased and glucagon and secretin decreased the frequency of spike potentials in the sphincter of Oddi and duodenum. Acetylcholine was associated with the largest increase in spike potentials in both the sphincter of Oddi and duodenum. Although there was variation in the number of pressure elevations related to sphincter of Oddi spike potentials, the baseline pressure remained constant during administration of the hormones. Acetylcholine infusion increased the biliary and pancreatic pressures to 29 and 31 mmHg respectively ($p < 0.01$). We conclude that gastrointestinal hormones may have an important role in regulating the excretion of bile and pancreatic juice into the duodenum.

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CHAPTER 5

GASTROINTESTINAL MYOELECTRIC ACTIVITY FOLLOWING ABDOMINAL OPERATIONS IN THE OPOSSUM

5.1. INTRODUCTION

The period of fasting after abdominal operations is subject to wide variation, mainly owing to the controversy concerning the duration of postoperative ileus. Some authors have reported that ileus inevitably follows the most trivial intra-abdominal procedures or even a simple pinching of the skin over the abdominal wall (1,2). However, others have described normal intestinal motility after most abdominal operations, including cholecystectomy and transection and anastomosis of the small bowel (3,5). These conflicting results may be related to different animals and techniques employed, such as clinical evaluation, balloon kymography, radiographic techniques, and intraluminal pressure measurements (6,7).

Recent developments of electromyography have allowed a more precise evaluation of gastrointestinal tract motility. In 1969, Szurszewski described the occurrence of a specific pattern of myoelectric activity in the gastrointestinal tract of the fasted dog (8). Others have confirmed this recurring activity, referred to as myoelectric migrating complex (MMC), in the fasting state of humans, dogs, opossums, and other animals (9-11). A few studies have been

reported on the effect of abdominal operations on the MMC (5,12,13). However, the myoelectric pattern of the stomach, small bowel, and the sphincter of Oddi after feeding has not been studied during the immediate postoperative period. Gastrointestinal and sphincter of Oddi motility disturbances during both the fasting and the fed states may occur after abdominal operations. Our objective in the present study is to evaluate the effect of abdominal operations on the sphincter of Oddi and gastrointestinal myoelectric activity both in the fasting and fed states.

5.2. MATERIAL AND METHODS

The myoelectric activity of the stomach, small bowel, and sphincter of Oddi of the opossum was studied postoperatively to determine the time of appearance of MMC following abdominal operations. The myoelectric pattern after feeding was also analyzed immediately after the appearance of the MMC.

Six opossums of either sex weighing 2.5 to 4.0 kg, were anesthetized with 25 mg of sodium pentobarbital per kg administered intraperitoneally. Upper midline laparotomy was performed and 7 pairs of bipolar electrodes were implanted in the sphincter of Oddi, gastric antrum, duodenum, proximal jejunum, midjejunum, terminal jejunum, and terminal ileum. In the antrum, the electrode pair was placed 3 cm proximal to the pylorus, and in the duodenum, the electrodes were fixed 3 cm distal to the sphincter of Oddi-duodenal

junction. The electrodes consisted of stranded silver-plated copper wire with teflon insulation of 36 American Wire Gauge size. The wires were soldered to a female connector.

A gastrostomy was performed with silastic tubing (1/16 inch inner diameter and 1/8 inch outside diameter) in the anterior gastric wall, 2 cm distal to the esophagogastric junction. The gastrostomy tube and the electrode wires were passed through a subcutaneous tunnel to the back of the animal. The abdominal wall was closed and the socket and the gastrostomy tube were fixed to the skin.

Control recordings were begun 7-10 days after implantation of the electrodes. The animals were fasted 15 hours before the studies. Three recording sessions of 4 to 6 hours were performed in each animal.

After the control recordings had been obtained, the abdomen was reopened through the previous incision. The small bowel was exteriorized and handled continuously for 5 min, 1 hour, or 3 hours. The selection of the procedure time was randomized. The intestines were then returned to the abdomen and the incision closed. Electromyographic recordings were performed in the fasted animals immediately after the operation and on each subsequent day until normal MMC's were detected for 2 consecutive days.

After complete recovery from the surgery, the same procedure was repeated on 2 additional occasions with different laparotomy times. Thus, each animal was subjected to 3 different procedures, a 5-min, a 1-hour, and a 3-hour

operation. The interval between the operations was 10-18 days.

Finally, 4 of the 6 opossums were subjected to terminal ileum transection with immediate end-to-end anastomosis. The small intestine was manipulated until 1 hour of operation was completed.

In order to study the electromyographic pattern after feeding, food at 20 Cal/kg consisting of equal parts of fat, protein, and carbohydrates was instilled into the stomach during phase I of the MMC. Ten control recording sessions were obtained 7-10 days after implantation of electrodes, and 10 other recordings were performed on the same day that the MMC was first seen after the abdominal operations. Studies included recordings of the fed pattern and at least one MMC preceding and following it. In 4 experiments, food was infused before the appearance of the MMC.

Five additional opossums were subjected to section of the duodenum 1 cm distal to the pylorus, closure of the duodenal stump, and gastrojejunal anastomosis. Electrodes were implanted as previously described. The time for this procedure was 1 hour. Again, the same type of recording was obtained from each of the 5 animals.

Electromyographic activities were recorded on an 8-channel Gould 2800S instrument (Gould Inc., Recording Systems Division, Cleveland, Ohio). For each recording session, a male socket connected through isolation preamplifiers to the recording system was plugged into the

animal socket. Recordings were made using a paper speed of 1 mm/s, low frequency cut-off filter of 1 hertz (Hz), high frequency cut-off filter of 10 Hz, and overall sensitivity of 25 or 50 millivolts (mV).

The recordings were analyzed to determine the postoperative time of the appearance of the MMC, the duration of the MMC, and the activity pattern after feeding. The MMC was divided into 4 phases as described by Code and Marlett (14). The myoelectric activity of the sphincter of Oddi was also divided into 4 phases and correlated with the MMC phases in the duodenum.

5.3. RESULTS

Fasting Pattern

Slow waves were easily identified in all sites studied in most of the recordings and their frequencies were constant before and after the MMC appearance. The average frequency of slow waves in the antrum was 3.5/min, 19/min in the duodenum, and 17/min in the terminal ileum. The frequency of slow waves in the sphincter of Oddi was the same as in the duodenum.

The MMC was considered present only when the 4 phases were identified (Figure 1); it migrated distally and its duration was within the range observed in the control recordings, i.e., 66-120 min with an average of 89 ± 16 min (mean $\pm$ 1SD). In all 5 animals with gastrojejunostomy, phase III migrated from the duodenum to the efferent loop of the

Figure 1. Migrating myoelectric complex phases (P) of the gastric antrum (A), sphincter of Oddi (SO), duodenum (D), and terminal ileum (I).

gastrojejunoscopy and down to the ileum. The frequency of sphincter of Oddi spike potentials correlated with the MMC phases in the duodenum in all animals after the appearance of the MMC.

Time of appearance of the MMC after the abdominal operations varied from immediately after the surgery to the fifth postoperative day and depended on the type and duration of the surgical procedure (Table 1). It was longer after the 3-hour laparotomy than after the 5-min laparotomy, and longer after gastroenterostomy than enteroenterostomy or laparotomy with 1-hour intestine handling.

During the time interval between the operation and the MMC appearance, 2 patterns of electromyographic recordings were observed. The most common pattern (75% of the instances) was the presence of multiple bursts of spike potentials on each slow wave of the duodenum, jejunum, and ileum (Figure 2). The amplitude of these spikes (8-20 mV) was discretely smaller than those observed later during phase III of the MMC (15-30 mV). These bursts lasted from 20 min up to 2 hours and were alternate with quiescent periods. Unlike phase III, these periods of intense activity did not migrate distally.

The second pattern (25% of the instances) was characterized by prolonged periods of quiescence with occasional spikes of low amplitude (5-10 mV) in the duodenum, jejunum, and ileum (Figure 2). Rare spike potentials were observed in the antrum in both patterns.

Table 1

Time of Appearance of MMC after Abdominal Operations

Type of Operation	Same day	Day 1	Day 2	Day 3	Day 5
5-min intestine handling	5	1	-	-	-
1-hour intestine handling	2	3	1	-	-
3-hour intestine handling	-	2	3	1	-
Enteroenterostomy	2	2	-	-	-
Gastrojejunostomy	-	-	-	3	2

Figure 2. Myoelectric recordings of the jejunum of 2 opossums obtained after laparotomy and before the appearance of the myoelectric migrating complex. Slow waves with only occasional spikes of slow amplitude can be observed in recording A. Multiple bursts of spike potentials on each slow wave are shown in recording B.

Spike potentials in the sphincter of Oddi were always present and their frequency was more constant than in the intestine and varied from 0.5 to 2.0 spikes/min. Spike potential amplitude in the sphincter of Oddi (10-15 mV) was constant for the same experiment.

Fed Pattern

In 8 of 10 experiments, the administration of food into the stomach abolished the MMC phases and caused the appearance of a fed pattern within 1 to 3 min. The duration of the fed pattern (239 ± 25 min) after the appearance of the MMC was similar to the control studies (227 ± 26 min).

The fed pattern was absent or delayed in 2 animals after infusion of food into the stomach on the first day of the MMC appearance. In one of these animals, the fed pattern was present on the second day of the MMC appearance; however, in the other animal, feeding activity continued to be delayed for 3 subsequent days. Later, a subhepatic abscess was drained from this animal. Interestingly, a normal MMC in the stomach and small bowel had been observed in this opossum since the fifth postoperative day. Food administration resulted in a fed pattern only in 72 min in the proximal jejunum (normal, 5 min) and 60 min later in the midjejunum (normal, 5-10 min).

The fed pattern did not occur for at least 2 hours in all 4 experiments in which food was infused before the appearance of the MMC. Vomiting did not occur in these

animals.

5.4. DISCUSSION

Developments in electromyographic techniques have allowed a better understanding of the gastrointestinal tract motility. Characteristic patterns of myoelectric activity occur during fasting and fed states in several species (9,15,16). The MMC originates in the stomach and propagates distally to the terminal ileum. It is present during the fasting state and the function of its activity front (phase III) is propulsion of gastrointestinal content between meals (17). After feeding, the MMC is substituted by the fed pattern.

Time of appearance of the MMC after abdominal operations has been suggested to correlate with the return of normal gastrointestinal motility (3,5). In the present study, administration of food on the first day that the MMC was observed after the operation usually resulted in a normal fed pattern. In addition, fed pattern was not seen when food was infused before the MMC appearance. However, the fed pattern was absent or delayed in 2 animals in which food was given on the first day of MMC appearance. One of the animals later proved to have a subhepatic abscess. These findings suggest that the presence of MMC is necessary to have a normal fed pattern. However, absent or delayed fed pattern may occur in animals that have normal MMC, as in the instance of the opossum with intra-abdominal abscess.

Time of appearance of the MMC after abdominal operations varied with the type and duration of the surgical procedures. Procedures that severed the upper gastrointestinal tract disrupted the MMC for longer periods of time. The time of appearance of the MMC was proportional to the duration of the operation.

The results from this study support the view that intestinal motility is not depressed for prolonged periods of time after abdominal operations. The MMC was observed within 24 hours after the operations in most experiments.

The opossum exhibits a myoelectric activity of the gastrointestinal tract similar to that of humans, dogs, and other animals during both the fasting and fed states (9,15,16). Therefore, it is possible that the opossum myoelectric activity during the postoperative period may also be similar to that of humans. In fact, Rothnie and associates described normal gastrointestinal transit of radiopaque material in humans 24 hours after various types of abdominal operations (6). They contend that the small bowel is capable of mixing and propelling after surgery and that the absence of postoperative bowel sounds is not due to a lack of intestinal motility but probably to the absence of content. Carmichael et al. reported that neither cholecystectomy nor transection and anastomosis of the intestine had any inhibitory effects on the myoelectric activity of the small bowel of dogs (5).

The role of analgesics and anesthetics in the

development of postoperative ileus needs to be evaluated. Morphine has been demonstrated to cause constipation, delayed gastric emptying, and a prolonged depression of intestinal propulsion (18). Bueno et al. reported no important change in the intestinal myoelectric activity of rats during anesthesia with ethyl ether, pentobarbital, or thiopental (13).

It has been suggested by combined electromyography and cineradiography that sphincter of Oddi spike potentials in the opossum are associated with peristaltic contractions of the sphincter of Oddi which would have the function of transporting bile and pancreatic juice into the duodenum (19). The frequency of spike potentials in the sphincter of Oddi varies with the MMC phases in the duodenum and with the feeding activity state (11,20).

Our study showed that the frequency of sphincter of Oddi spike potentials was rather constant and low before the MMC appearance in the postoperative period. Correlation between the sphincter of Oddi activity and the MMC phases in the duodenum was reinstated with the MMC appearance.

The presence of multiple bursts of spike potentials on each slow wave of the small bowel observed postoperatively in most experiments is probably due to intestine irritation secondary to handling of the small bowel and placement of electrodes. Multiple incoordinate contractions of the intestine were observed during manipulation of the small bowel at the operations.

We conclude from this study that the return of gastrointestinal motility following abdominal operations depends on the type and duration of the surgical procedure. Intestinal motility is normal within 24 hours following surgery in most instances. Feeding does not produce a fed pattern in the absence of MMC. Disturbances of the fed pattern may occur in the presence of intra-abdominal sepsis, even in animals with normal MMC.

5.5.SUMMARY

Gastrointestinal myoelectric activity of the opossum, both in fasting and fed states, was studied after abdominal operations. Five different procedures were performed: a 5-min, a 1-hour, and a 3-hour laparotomy with intestinal handling, enteroenterostomy, and gastrojejunosomy. Electromyographic recordings from the stomach, duodenum, jejunum, ileum, and sphincter of Oddi were obtained from unanesthetized animals. A normal fasting pattern after abdominal operations was observed from immediately after surgery to the fifth postoperative day and depended on the type and duration of the surgical procedure. A fed pattern did not occur in the experiments in which food was instilled before the appearance of the myoelectric migrating complex. A normal fed pattern was observed after the myoelectric migrating complex appearance in all but 2 experiments, one of which occurred in an animal with an intra-abdominal abscess.

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CHAPTER 6

EFFECT OF ALCOHOL UPON MYOELECTRIC ACTIVITY OF THE GASTROINTESTINAL TRACT AND PANCREATIC AND BILIARY DUCT PRESSURES

6.1. INTRODUCTION

Alcohol is responsible for two-thirds of the instances of pancreatitis in charity hospitals and for one-third in private hospitals (1). The mechanism by which alcohol produces damage to the pancreas remains unknown. Some authors suggest that alcohol may induce spasm of the sphincter of Oddi and, thereby, produce an increase in the pancreatic duct pressure (2,3). This intraductal pressure elevation could disrupt pancreatic ductules leading to liberation and activation of pancreatic enzymes causing autodigestion and inflammation of the pancreas.

Recent developments in electrophysiologic techniques have allowed a more direct evaluation of the dynamics of the sphincter of Oddi (4,5). However the effect of alcohol upon electromyography of the sphincter of Oddi has not been systematically evaluated. We have developed a method that allows simultaneous measurements of pancreatic and biliary pressures and recording of the sphincter of Oddi myoelectric activity. This method allows pressure recording for several weeks and avoids interference with the flow of bile and pancreatic juice into the duodenum. The present

investigation was done to evaluate the effect of alcohol upon myoelectric activity of the gastrointestinal tract and upon pancreatic and biliary duct pressures.

6.2. MATERIAL AND METHODS

Twelve opossums weighing 3.0 to 4.5 kg were fasted overnight and then anesthetized with intraperitoneal administration of 25 mg/kg of sodium pentobarbital. Upper midline laparotomy was performed.

The sphincter of Oddi of the opossum is mostly extraduodenal and measures 2 to 3 cm in length. The main pancreatic duct joins the common duct at the proximal portion of the sphincter of Oddi to form a common channel.

The main pancreatic duct was identified in the head of the pancreas and catheterized with a PE-50 polyethylene T tube. A PE-50 polyethylene tube was placed in the common duct through a small bile duct that connected the right lateral lobule of the liver to the common duct. This method allowed pressure recordings for several weeks with no interference of sphincter of Oddi function or the flow of bile or pancreatic juice into the duodenum.

Six pairs of bipolar extracellular electrodes were implanted in the antrum, duodenum and sphincter of Oddi; two in each site. In the antrum, the electrode pairs were placed 4 and 3 cm proximal to the pylorus. In the duodenum, the electrodes were fixed at 2 cm proximal and 2 cm distal to the sphincter of Oddi-duodenal junction. Sphincter of Oddi

electrodes were placed 1 and 2 cm proximal to the sphincter of Oddi-duodenal junction. The electrodes consisted of stranded silver-plated copper wire with teflon (polytetrafluoroethylene) insulation of 36 AWG (American Wire Gauge) size.

A gastrostomy and duodenostomy were performed with silastic tubing 4 cm proximal and 2 cm distal to the pylorus, respectively. The four tubes (biliary, pancreatic, gastrostomy, and duodenostomy) and the electrode wires were previously passed through a subcutaneous tunnel from the back of the opossum to the abdomen. The wires were soldered to a female socket prior to the operation. The socket and the tubes were stitched to the skin of the back of the animal.

An eight channel Gould 2800S instrument (Gould Inc., Recording Systems Division, Cleveland, Ohio) was used to record the electromyographic activities and pressures. A male socket connected to the recording instrument through isolation preamplifiers was plugged into the back socket of the opossum for each recording session. Electromyographic recordings were made using a paper speed of 1 mm/sec, low frequency cut-off filter of 1 Hz, high frequency cut-off of 10 Hz and over-all sensitivity of 100 mV.

The pancreatic and biliary catheters were attached to Gould P23 pressure transducers (Gould Statham Instruments, Inc., Hato Rey, Puerto Rico) which were infused with water at a constant rate of 0.04 ml/min. An Arndorfer hydraulic

capillary infusion system (Arndorfer Medical Specialities, Inc., Greendale, Wisconsin) was used to administer the water. The low frequency cut-off filter was positioned at direct current offset and the high frequency cut-off filter was set at 10 Hz or at mean (M) position. In order to eliminate the pressure secondary to the resistance to water flow, catheters equal to those placed in the pancreatic and biliary ducts were perfused with water at a flow rate of 0.04 ml/min. The tip of each external catheter was placed at the same height as the internal catheters while the opossum was on its abdomen.

The pressure recorded from the external catheters was considered to be zero level. The sensitivity of the pressure recording system was tested by occluding the tip of each catheter for two seconds. This caused an increase in pressure of at least 20 mmHg.

Recordings were begun seven to ten days after the operation. All studies were performed on conscious, fasted opossums. During each recording session, at least one normal migrating myoelectric complex (MMC) was recorded as control. Ethanol at concentrations of 10, 20 or 40% and in volumes of 1 or 2 ml/kg was then administered into the stomach (20 experiments) or into the duodenum (45 experiments).

Bolus alcohol instillations were performed during phase I of the MMC in 55 experiments and during phase II in ten experiments. Recordings were continued for one or two additional MMCs. Sodium chloride solution (154 mEq/l) or

distilled water was also infused at volumes of 1 or 2 ml/kg through the gastrostomy or duodenostomy tubing (ten experiments). In ten other experiments, alcohol was instilled for a second or third time during the same or subsequent MMC.

The myoelectric activity of the stomach and duodenum was divided into four phases (6). In phase I, occasional or no spike potentials are observed. During phase II, the spike potentials are irregular and increase in frequency and intensity throughout the phase. Phase III is characterized by action potentials of high amplitude that are superimposed on 90 to 100% of the slow waves. During phase IV, the frequency and intensity of spike potentials subside quickly to quiescence in phase I, therefore beginning a new cycle.

The sphincter of Oddi of the opossum exhibits cyclic changes in the frequency of spike potentials that correlate with the MMC cycle in the duodenum and therefore, myoelectric activity of the sphincter of Oddi was also divided into phases I, II, III and IV. The number of slow waves with spike potentials was determined for each of the MMC phases. The data were analyzed statistically by means of the Student's two-tailed, paired t test.

6.3. RESULTS

The control MMC phases of the sphincter of Oddi and duodenum are shown in Figure 1. Instillation of alcohol caused a characteristic myoelectric activity sequence

Figure 1. Myoelectric migrating complex phases (P) of the sphincter of Oddi (SO) and duodenum (D).

(Figure 2). In the duodenum, a minute burst of spike activity (10/min) was followed by five to ten minutes of absent or occasional spikes. A vigorous phase III-like activity (16 spike bursts/min) then ensued in 59 instances (91%). Finally, a new MMC with (nine instances) or without phase I (47 instances) occurred. In six studies (9%), the initial burst of spike activity was followed by phase II of a new MMC without early appearance of phase III-like activity.

A significant increase in the number of spike potentials occurred for 15 to 20 minutes in the sphincter of Oddi in all instances (7.4 spike bursts/min). The two largest increases in the frequency of sphincter of Oddi action potentials occurred in the first minute after alcohol instillation (8.2 spike bursts/min) and simultaneous with phase III-like activity in the duodenum (8.1 spike bursts/min). This sequence of changes in the duodenum and sphincter of Oddi myoelectric activity occurred after instillation of alcohol into either the stomach or duodenum.

The appearance of spike activity in the antrum was variable, depending upon the location of alcohol instillation. It was observed immediately after gastric administration and six to eight minutes after duodenal instillation. The initial burst of spike activity observed in the duodenum and sphincter of Oddi after duodenal administration of alcohol was not seen in the antrum.

Appearance of phase III-like activity was independent

Figure 2. Effect of alcohol on myoelectric activity of the proximal (SO_1) and distal (SO_2) sphincter of Oddi and duodenum (D). Phase III-like activity (III) can be seen eight minutes after 20 per cent alcohol administration (ETOH) into the duodenum. A five minute recording period was deleted (//).

of the dosage and concentration of the alcohol administered and of the MMC phase that alcohol was instilled. The comparison between the MMC that preceded alcohol administration and the MMC that followed phase III-like activity is given in Table 1. Phase I was not observed in the MMC after alcohol insitillation in 84% of the experiments. Administration of isotonic sodium chloride solution or distilled water did not alter the normal pattern of the MMC.

A second or third instillation of alcohol caused a transient increase in the number of spike potentials in the duodenum and antrum in eight of ten experiments (80%), but no subsequent phase III-like activity was observed. Phase III-like activity appeared after additional alcohol administration in only two experiments (20%). However, there was a marked subsequent increase in the spike burst activity of the sphincter of Oddi in all instances (7.3 spike bursts/min).

Two types of pressure changes in the pancreatic and biliary ducts were recorded. First, pressure oscillation of 1 to 3 mmHg were observed with respiratory movements. These pressure variations could be eliminated from the recordings by turning the high frequency cut-off filter knob to the M position. Second, there was a temporary elevation of pancreatic and biliary pressures of 1 to 3 mmHg simultaneous with each sphincter of Oddi spike potential.

There was an increase in the number of pressure

Table 1

Myoelectric Activity of the Antrum, Duodenum and Sphincter of Oddi

	Myoelectric migrating complex phase			
	No. of spike potentials (spikes/min)			
	I	II	III	IV
Control MMC				
Antrum	0	1.9±0.6	3.3±0.8	1.5±0.3
Duodenum	0	6.1±2.3	15.5±1.0	5.9±2.3
Sphincter of Oddi	2.8±1.1	4.6±0.9	5.8±0.5	3.2±0.9
Duration (min)	20.2±4.8	50.8±8.1	8.0±0.7	4.9±0.6
MMC after phase III-like activity				
Antrum	§	2.2±0.9*	3.2±0.9	1.4±0.5
Duodenum	§	6.1±1.9	15.2±1.1	4.3±1.9**
Sphincter of Oddi	§	4.8±1.2	6.2±0.7**	2.8±1.1
Duration (min)	§	54.1±6.5	6.4±0.6	4.2±0.9

§ Alcohol administration in phase I.

* This value is significantly greater than the corresponding value in the column above at the 5 per cent level, $p < 0.05$.

** This value is significantly greater than the corresponding value in the column above at the 1 per cent level, $p < 0.01$.

elevations related to sphincter of Oddi spike-burst potentials after alcohol administration, but baseline pressures remained constant. The mean pancreatic and biliary baseline pressures before alcohol instillation were 15.0 ± 3.8 and 14.0 ± 3.6 mmHg, respectively; after ethanol administration, they were 17.0 ± 2.7 and 14.0 ± 2.8 mmHg.

6.4. DISCUSSION

The MMC is a specific pattern of myoelectric activity of the gastrointestinal tract that was first described in fasted dogs in 1969 (7). It is observed only during the fasting state in some species and during fasting and fed states in others. Human beings, dogs and opossums are included in the first group and sheep and cattle are in the second group (5,8). It has been shown that the MMC is composed of four phases which propagate caudad from the stomach to ileum and recur cyclicly (6). The frequency of spike potentials increases from phase I through phase III, then decreases during phase IV to begin a new myoelectric complex.

The results of our study and those of another study have demonstrated that the sphincter of Oddi of a fasting opossum exhibits cyclic changes in the number of spike potentials that correlate with the MMC in the duodenum (5). However, the number and intensity of spike potentials in the sphincter of Oddi are different from those of the duodenum.

The function of recurrent MMC in the gastrointestinal

tract is unknown. It has been demonstrated by cineradiography that the activity front of each complex is associated with propagated contraction whose function is propulsion of gastrointestinal content between meals (9). It also has been suggested by combined electromyography and cineradiography that sphincter of Oddi spike potentials in opossums are associated with peristaltic contractions of the sphincter of Oddi which would have the function of transporting bile from the sphincter of Oddi into the duodenum (10).

While an association between alcoholism and pancreatitis is well established, little is known about the pathogenesis of alcoholic pancreatitis. It has been suggested that alcohol may cause irritation and spasm of the sphincter of Oddi (2,3). An increase in pancreatic pressure might rupture pancreatic ducts, thereby liberating proteolytic enzymes and that might autodigest the pancreas. Unfortunately, this attractive hypothesis has, to date, no scientific validity. Spasm of the sphincter of Oddi has been detected by indirect methods, such as duct pressure measurement and evaluation of the volume of pancreatic secretion in the duodenum. However, the results of these studies have been controversial (11-14).

Electromyographic studies provide a more direct evaluation of sphincter of Oddi activity. Our experimental model combines recording of sphincter of Oddi myoelectric activity and measurement of pancreatic and biliary duct

pressure under circumstances that minimally disturb the normal pancreatobiliary physiologic characteristics.

Systematic electromyographic evaluation of the influence of alcohol on the sphincter of Oddi has not been previously reported. An increase in the number and amplitude of spike potentials in the sphincter of Oddi in a rabbit after alcohol administration has been described, but the influence of the phases of the MMC was not accounted for (15).

The results of our study have demonstrated that gastric or duodenal instillation of alcohol during phase I or II of the MMC causes a phase III-like activity in the antrum, duodenum and sphincter of Oddi in five to ten minutes. This phase III-like activity was similar to the normal MMC phase III in duration and number and amplitude of spike potentials. Subsequent alcohol administration in the same or following MMC produced a dramatic increase in the sphincter of Oddi spike potentials without causing phase III-like activity in the duodenum.

The results of previous reports suggest that MMC gastrointestinal tract activity is coordinated by motilin since the MMC phase correlates with cyclic changes of the plasma motilin (16). The peak of motilin was shown to occur concurrently with phase III in the duodenum. The occurrence of premature phase III after administration of morphine sulfate intravenously has recently been observed (17). However, administration of morphine sulfate during the

initial 20% of the MMC cycle did not begin premature phase III, even at supramaximal doses. As the remainder of the MMC cycle progressed, premature phase III was initiated with diminishing doses of morphine.

Alcohol, as used herein, induced phase III-like activity independent of the MMC phase in which alcohol was instilled. The average amount of alcohol administered was comparable with a 70 kg person drinking 15 g of ethanol. Therefore, it is possible that repetitive increases in the myoelectric activity of the sphincter of Oddi that may occur with chronic ingestion of alcohol may be an important contributory factor in the pathogenesis of alcoholic pancreatitis.

There was an increase in the number of pressure elevations related to sphincter of Oddi phase III-like activity after alcohol instillation, but baseline pressure remained constant. The pancreatic and biliary pressures were also not increased during normal phase III. On the contrary, biliary and pancreatic pressure elevations after alcohol administration in the dog has been described (18). These conflicting results may be related to different recording techniques and species used.

We conclude that gastric and duodenal instillation of alcohol causes a dramatic increase in the number of spike potentials in the antrum, duodenum and sphincter of Oddi and the onset of phase III-like activity. Subsequent alcohol administration in sequence evoked intense spike potentials

in the sphincter of Oddi without causing phase III-like activity in the antrum and duodenum. These alcohol-related myoelectric disturbances may contribute to abnormal function of the ampulla of Vater. There was no change in the baseline pressure after alcohol administration.

6.5. SUMMARY

Myoelectric activity of the antrum, duodenum and sphincter of Oddi was recorded from 12 conscious opossums. The common duct and the pancreatic duct were cannulated for pressure measurements. Recordings were made in the fasted state and after gastric or duodenal administration of ethanol. Alcohol was instilled during phase I (55 experiments) or phase II (ten experiments) of the migrating myoelectric complex. Administration of alcohol caused the appearance of phase III-like activity in five to ten minutes in 91% of the experiments.

Pancreatic duct and common duct pressure oscillations occurred synchronously with respiratory movements and with sphincter of Oddi spike potentials. There was an increase in the number of pressure elevations related to the increase in sphincter of Oddi spike potentials after alcohol administration; however, baseline pressures remained constant. It is concluded that the administration of alcohol into the stomach or duodenum causes the appearance of phase III-like activity and that there is no change in the baseline pressure after the instillation of alcohol.

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CHAPTER 7

SPHINCTER OF ODDI AND GASTROINTESTINAL MOTILITY DISTURBANCES FOLLOWING ALCOHOL ADMINISTRATION IN THE OPOSSUM

7.1. INTRODUCTION

Szurszewski and others have described a characteristic pattern of myoelectric activity, referred to as the migrating myoelectric complex (MMC), which is present during the fasting state and propagates down the gastrointestinal tract cyclically from the stomach to the ileum (1,2,3). After feeding, the MMC is abolished and replaced with a feeding activity pattern in several species, including man, dog and opossum.

We have demonstrated previously that instillation of alcohol at concentrations of 10, 20, and 40% into the stomach or into the duodenum causes the appearance of intense spike potentials in the sphincter of Oddi and duodenum similar in frequency, duration, and amplitude to those observed in phase III of the MMC (4). There was an increase in the frequency of pressure elevations in the pancreatic duct and common bile duct related to the increase in sphincter of Oddi spike potentials following alcohol administration; however, the baseline pressures remained constant. Our objective in the present study is to evaluate the mechanism by which alcohol stimulates the motility of the sphincter of Oddi and duodenum. The effect of alcohol on

the gastric, duodenal, and jejunal mucosa of opossums that were subjected to gastrojejunostomy with duodenal exclusion were assessed to determine whether alcohol stimulates the motility of the sphincter of Oddi and duodenum by direct contact with the duodenal mucosa or not. The concentration of plasma motilin was also determined during the normal MMC phases and during phase III-like activity caused by alcohol.

7.2. MATERIAL AND METHODS

Seven opossums of either sex weighing 2.5 to 3.5 kg were subjected to an upper midline laparotomy following intraperitoneal administration of 25 mg of sodium pentobarbital per kg. The gastroduodenal junction was severed and a gastrojejunostomy with closure of the duodenal stump was performed (Figure 1).

Silastic catheters were placed into the stomach, duodenal stump, mid-jejunum, and jugular vein. Seven pairs of bipolar extracellular electrodes were implanted in the sphincter of Oddi, gastric antrum, duodenum, proximal jejunum, mid-jejunum, terminal jejunum, and terminal ileum. The electrodes consisted of stranded silver-plated copper wire with teflon insulation of 36 AWG size (Micro Measurement Co., Romulus, Michigan). The wires were placed in the muscular layer of the gastrointestinal tract and sphincter of Oddi through a 25-gauge hypodermic needle and the end was tied off. The catheters and the wires were passed through a subcutaneous tunnel to the back of the

Figure 1. Schematic diagram of the opossum preparation showing the gastrojejunostomy, the electrodes, and the gastric and duodenal stump catheters.

animal. The wires were previously soldered to a female socket. The catheters and the socket were stitched to the skin.

Experiments were begun seven to ten days after the operation and were performed on awake, nonmedicated animals. Electromyographic activities were recorded on an eight-channel Gould 2800S instrument (Gould Inc., Recording Systems Division, Cleveland, Ohio). For each recording session, a male socket connected to the recording system was plugged into the animal socket.

Bolus infusions of a 20% solution of ethanol in a volume of 2 ml/kg of body weight were given into the stomach (30 experiments), duodenal stump (30 experiments), jejunum (ten experiments) and intravenously (40 experiments) 20 minutes after the beginning of phase I of the MMC in the duodenum. Each experiment included recording of the MMC in which alcohol was instilled and the MMC preceding it.

The following solutions were also administered into the duodenum of three additional opossums at a volume of 2 ml/kg, nine experiments of each: sodium chloride (154 mEq/liter), 20% glucose (isocaloric to 20% ethanol; 0.8 Cal/min) and 32% glycerol (iso-osmolar to 20% ethanol; 5.8 molar/liter). Alcohol blood level was determined before and following duodenal and intravenous infusion of ethanol on different days (eight experiments of each). The blood was drawn during the appearance of phase III-like activity following infusion of alcohol into the duodenum or 20

minutes after intravenous administration of alcohol. Alcohol was determined by a DuPont Automatic Clinical Analyzer (DuPont Co., Wilmington, Delaware) that employed a modified alcohol dehydrogenase enzymatic procedure.

Plasma motilin concentration was determined in five other opossums. In these studies, 5 ml samples of venous blood were obtained from the jugular catheter during phases I, II, and III of the control MMC and during phase III-like activity that followed duodenal instillation of alcohol, 16 samples of each. The samples were drawn ten minutes after the beginning of phases I and II and two minutes after the beginning of phases III and III-like activity. The plasma was separated by refrigerated centrifugation for radioimmunoassay of motilin. The red blood cells with equal volume of normal saline solution were returned to the animals. Motilin assays were performed in Dr. William Y. Chey's laboratory in Rochester, New York by a method described previously (5).

The MMC was divided into four phases as described by Code and Marlett (6). The frequency of slow waves with spike potentials was determined for each MMC phase and following alcohol instillation. The data were analyzed statistically by means of analysis of variance.

7.3. RESULTS

Control Migrating Myoelectric Complex

The frequency of slow waves was $3.5 \pm 0.2/\text{min}$ (mean $\pm$

1SD) in the antrum, $19 \pm 0.3/\text{min}$ in the sphincter of Oddi and duodenum, $18 \pm 0.3/\text{min}$ in the proximal jejunum, and $14 \pm 0.4/\text{min}$ in the terminal ileum. The frequency of slow waves with spike potentials in the sphincter of Oddi, antrum, duodenum, proximal jejunum, and terminal ileum and the duration of each MMC phase in the duodenum are shown in Table 1.

No spike potentials were seen in the antrum and small intestine during phase I. However, spikes were always present in the sphincter of Oddi. In all sites, the frequency of spike potentials increased throughout phase II to reach a maximum during phase III and then decreased rapidly during phase IV to start a new MMC. Even though the gastroduodenal junction was severed, the activity front of the MMC (phase III) was seen first in the duodenum, and then migrated to the efferent loop of the gastrojejunostomy and to the terminal ileum.

Myoelectric Activity Following Alcohol Administration

Intraduodenal administration of ethanol provoked a minute of spike potentials ($10/\text{min}$) in the duodenum that was followed by four to eight minutes of no spike activity. After this period, phase III-like activity occurred in 26 experiments (87%). This vigorous spike activity was similar to phase III of the MMC in frequency (16 bursts of spikes/min), duration (6-8 min), and amplitude (10-15 mV) of the bursts of spike potentials. A significant increase in the number of spike potentials (7.2 bursts of spikes/min)

Table 1

**Myoelectric Activity of the Sphincter of Oddi
and Gastrointestinal Tract During Fasting**

Spike Activity Frequency (bursts of spikes/min)	Myoelectric Migrating Complex Phases			
	I	II	III	IV
Sphincter of Oddi	1.3±0.3	3.7±0.6	4.4±0.6	2.9±0.5
Antrum	0	1.7±0.3	2.5±0.4	2.0±0.4
Duodenum	0	4.2±1.1	17.3±0.6	4.5±1.3
Jejunum	0	5.9±1.2	15.8±0.7	6.1±1.9
Ileum	0	3.9±0.9	14.1±0.5	3.7±0.9
Duration (min)*	38.6±6.1	39.0±5.7	7.6±0.4	6.2±0.5

*Duration of each phase in the duodenum

occurred in all studies for 15 to 20 minutes in the sphincter of Oddi. The two largest increases were observed immediately after alcohol administration (8.1 bursts of spikes/min). Only occasional spike potentials were observed in the antrum following instillation of alcohol into the duodenum.

Instillation of alcohol into the stomach resulted in phase III-like activity in six to eight minutes in 20 experiments (67%) (Figure 2). A regular phase I (60%) or phase II (40%) of the MMC then followed. The duration of phases II (42.4 ± 8.2 min) (mean $\pm$ 1SD), III (7.4 ± 0.3), and IV (5.8 ± 0.6) following alcohol instillation was similar to the control phases II (39.0 ± 5.7), III (7.6 ± 0.4), and IV (6.2 ± 0.5).

Moderate spike activity (six bursts of spikes/min) was observed in the jejunum for one to two minutes after administration of alcohol into the mid-jejunum, but no change in spike activity occurred in the sphincter of Oddi and duodenum.

Intravenous infusion of alcohol caused phase III-like activity in the sphincter of Oddi and duodenum in nine experiments (22%). This vigorous spike activity was observed 15 to 20 minutes after administration of alcohol and occurred in only one animal. No change in spike activity of the sphincter of Oddi and gastrointestinal tract followed intravenous infusion of alcohol in the other six animals.

Phase III-like activity always migrated distally to the

Figure 2. Electromyographic recording of the sphincter of Oddi (SO), duodenum (D), and antrum (A) during phase I of the migrating myoelectric complex of an opossum with gastro-jejunosomy and duodenal exclusion. A 20% solution of ethanol in volume of 2 ml/kg infused into the stomach (ETOH) caused immediate spike activity in the antrum. Intense spike activity was also observed in the sphincter of Oddi and duodenum in ten minutes. A six-minute recording period was deleted from the figure (/).

proximal jejunum where it was seen 15 to 20 minutes after the regular phase III. Only one activity front was observed in the distal jejunum and ileum.

Administration of solutions of sodium chloride and glucose caused no or occasional bursts of spike potentials in the duodenum and sphincter of Oddi. Glycerol instillation provoked immediate, intense bursts of spike potentials in the duodenum (12/min), sphincter of Oddi (8/min) and proximal jejunum (11/min) for two to six minutes. This initial period of spike activity was not followed by phase III-like activity. A normal phase I or II of the MMC ensued.

Alcohol blood level after duodenal and intravenous instillation of ethanol was 45 ± 29 and 190 ± 17 mg/dl, respectively. No phase III-like activity occurred in the eight experiments in which alcohol was administered intravenously. The ethanol level before administration of alcohol was always below 10 mg/dl, which is the lowest value determined by the method employed.

Plasma Motilin Concentration

The peak of plasma motilin level observed during the control MMCs occurred during phase III (35.6 ± 4.7 pM/ml; mean $\pm$ 1SE), which was significantly greater than the concentration obtained during phase II (20.6 ± 5.1) ($p < 0.05$), but not different from the values obtained during phase I (30.5 ± 7.6). There was no difference in the concentration of plasma motilin obtained during the phase III-like activity (41.5 ± 4.6) and phase III of the MMC

(35.6 $\pm$ 4.7).

7.4. DISCUSSION

The effect of alcohol on the sphincter of Oddi has been subjected to several studies. It has been suggested that alcohol may cause spasm of the sphincter of Oddi and increase pancreatic pressure, which might rupture pancreatic ducts and cause liberation of proteolytic enzymes and pancreatitis (7,8). However, the motility of the sphincter of Oddi following gastroduodenal infusion of alcohol has been evaluated only by indirect methods, such as pancreatic duct pressure measurements and determination of the volume of pancreatic juice in the duodenum (9-12).

Recently, electromyography has been employed to study the motility of the sphincter of Oddi and gastrointestinal tract (13,14). The sphincter of Oddi in the opossum exhibited spontaneous spike potentials which propagated from the proximal to the distal portion of the sphincter. The myoelectric activity of the sphincter of Oddi is independent from that of the duodenum (13,14); however, the frequency of bursts of spike potentials in the sphincter of Oddi correlates with the phases of the MMC in the duodenum. Both sphincter of Oddi and duodenum frequencies of bursts of spikes increase from phase I through phase III and then decrease rapidly during phase IV to start a new MMC.

We have demonstrated in a previous study that instillation of alcohol into the stomach or into the

duodenum of the opossum causes a dramatic increase in the frequency of bursts of spike potentials in the sphincter of Oddi and duodenum (4). In order to further evaluate the mechanism by which alcohol stimulates the motility of the sphincter of Oddi and duodenum, ethanol was instilled on the gastric, duodenal, and jejunal mucosa or administered intravenously in opossums subjected to gastrojejunostomy with duodenal exclusion.

Instillation of alcohol into the stomach or duodenum caused both an initial burst of spike potentials and phase III-like activity in eight to ten minutes in the sphincter of Oddi and duodenum. Gastrojejunostomy with duodenal exclusion impeded direct contact of alcohol on the duodenal mucosa after administration of ethanol into the stomach and therefore, only a direct irritative effect on the sphincter of Oddi and duodenum does not explain the appearance of phase III-like activity. In addition, administration of hyperosmolar substance (glycerol) into the duodenum caused only the initial intense bursts of spike potentials in the duodenum and sphincter of Oddi, probably due to a direct irritative effect, but not phase III-like activity. The delay in appearance of phase III-like activity following alcohol instillation suggests that a humoral substance that may be released from the upper gastrointestinal tract mucosa is responsible for this myoelectric disturbance.

Since the level of plasma motilin has been demonstrated to correlate with the MMC phases (5,15), we have evaluated

the relationship of plasma motilin concentration with phase III-like activity caused by instillation of alcohol into the upper gastrointestinal tract. The concentration of plasma motilin was elevated during phase III-like activity and it was similar to the normal phase III of the MMC. This suggests that the phase III-like activity produced by administration of ethanol may be caused by the release of motilin from the upper gastrointestinal tract. The concentration of motilin during phase I was not significantly different from that seen during phase III, probably because the blood samples were obtained only ten minutes after the beginning of phase I, i.e., when the motilin concentration was still elevated following the peak during phase III.

Infusion of alcohol into the mid-jejunum caused no change in spike activity of the sphincter of Oddi and duodenum. In this instance, only a moderate spike activity was observed in the jejunum for one to two minutes. Intravenous administration of ethanol likewise did not change the pattern of spike activity of the sphincter of Oddi and gastrointestinal tract except in one animal. In addition, the occurrence of phase III-like activity did not correlate with the alcohol blood level.

We conclude from this study that instillation of alcohol into the stomach or duodenum produces intense bursts of spike potentials in the sphincter of Oddi and duodenum. There is no correlation between alcohol blood levels and

occurrence of this intense spike activity. The increase in motilin plasma level following instillation of alcohol suggests that phase III-like activity produced by instillation of alcohol may be caused by the release of motilin from the upper gastrointestinal tract. The relationship between pancreatitis and the repetitive occurrence of vigorous spike activity in the sphincter of Oddi and duodenum following chronic ingestion of alcohol needs to be evaluated.

7.5. SUMMARY

Myoelectric activity of the gastrointestinal tract and sphincter of Oddi was recorded in seven awake opossums. The animals were subjected to gastrojejunostomy with duodenal exclusion to study the effect of alcohol on the gastric, duodenal, and jejunal mucosa. The response to intravenous infusion was also evaluated. Radioimmunoassay of motilin was performed in five other opossums during phases I, II, and III of the control migrating myoelectric complex (MMC) and during the phase III-like activity following administration of alcohol. Phase III-like activity was observed following infusion of alcohol into the duodenum in 26 studies (87%), into the stomach in 20% (67%), and intravenously in nine (22%). Alcohol blood level after duodenal and intravenous instillation of ethanol was 45 and 190 mg/dl respectively (eight experiments of each). There was no difference in the concentration of plasma motilin obtained during phase

III-like activity (41.5 ± 4.6 pM/ml) and phase III of the MMC (35.6 ± 4.7). We conclude that instillation of alcohol into the stomach or duodenum produces intense bursts of spike potentials in the sphincter of Oddi and duodenum. There is no correlation between alcohol blood levels and occurrence of this intense spike activity.

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CHAPTER 8

EFFECT OF 16,16 DIMETHYL PROSTAGLANDIN E_2 ON THE MYOELECTRIC ACTIVITY OF THE GASTROINTESTINAL TRACT OF THE OPOSSUM

8.1. INTRODUCTION

Prostaglandins are substances derived from unsaturated fatty-acids which are widely distributed in several human tissues, including the gastrointestinal tract (1). The role of prostaglandins under physiological and pathological conditions in the gastrointestinal tract is currently under extensive evaluation. Prostaglandins have been shown to produce important disturbances in the motility of the gastrointestinal tract (1-3). The effects are variable and depend on the type of prostaglandins, the dose, the species, and the muscle layer studied (3-5). Prostaglandin E_2 and its methylated derivative, 16,16-dimethyl prostaglandin E_2 (16,16-dm PGE_2), cause diarrhea in several species including man (2,6).

It has been suggested that the mechanism by which prostaglandins cause diarrhea is due to changes in the gastrointestinal motility and/or in the transport of water and electrolytes across the intestinal mucosa (6,7). The effect of 16,16-dm PGE_2 on the migrating myoelectric complex in vivo has not been evaluated. Our objective in the present study is to assess the effect of 16,16-dm PGE_2 and indomethacin, an inhibitor of prostaglandin synthesis, on

the myoelectric activity of the gastrointestinal tract and sphincter of Oddi in the opossum.

8.2. MATERIAL AND METHODS

Seven opossums of either sex weighing 2.6 to 3.5 kg were fasted overnight and then anesthetized with intraperitoneal administration of 25 mg of sodium pentobarbital per kg. Upper midline laparotomy was performed.

Seven pairs of bipolar extracellular electrodes were implanted in the muscular layer of the sphincter of Oddi, distal gastric antrum, duodenum, proximal jejunum, midjejunum, terminal jejunum, and terminal ileum. The electrodes consisted of stranded silver-plated copper wire with teflon insulation of 36 AWG (American Wire Gauge) size. The other end of the wires was previously soldered to a female socket.

Following abdominal wall closing, a silastic catheter was inserted into the jugular vein. The catheter and the wires were passed through a subcutaneous tunnel to the animal's back and stitched to the skin.

Electromyographic recordings were started seven to ten days after the operation and were performed on conscious opossums fasted for 12 hours. For each recording session, a male socket which was connected to an eight-channel Gould 2800S instrument (Gould Inc., Recording Systems Division, Cleveland, Ohio) was plugged into the opossum socket.

Following recording of at least one control migrating myoelectric complex (MMC), 16,16-dm PGE₂ (Upjohn, Kalamazoo, Michigan) or indomethacin (Sigma Chemical Co., St. Louis, Missouri) was infused intravenously. In order to obtain a stock solution, 16,16-dm PGE₂ was dissolved in absolute ethanol, separated in small aliquots of 20 µg/ml, and frozen. For each experiment, the stock solution was diluted with 0.9 sodium chloride solution. Indomethacin solution was freshly prepared for each experiment by dissolving it in 5% sodium carbonate solution.

The 16,16-dm PGE₂ was administered continuously for one complete MMC cycle in the duodenum at a rate of 0.1 ml/min employing a Harvard pump. A total of ten experiments of each of the following doses of 16,16-dm PGE₂ was performed: 0.1, 1, 2 and 5 µg/kg/h. Bolus infusion of 2 µg/kg/h of 16,16-dm PGE₂ was also studied (ten experiments). In ten other experiments, indomethacin at a dose of 10 mg/kg, was infused as a bolus. All infusions were started at the beginning of phase I of the MMC in the duodenum. Following administration of each substance, at least two additional MMCs were recorded.

Each recording session lasted five to eight hours. For analysis of the myoelectric recordings, the tracings were divided into two-minute intervals and the average frequency of slow waves with superimposed spike potentials for each phase of the MMC was determined. The MMC was divided into four phases as described by Code and Marlett (8). Honda et

al. and our group have shown that there is a temporal correlation between the MMC phases in the duodenum and sphincter of Oddi (9,10). All phases in the sphincter of Oddi start almost simultaneously with the MMC phases in the proximal duodenum. Therefore, the myoelectric activity of the sphincter of Oddi was also divided into four phases. The duration of each MMC was determined by measuring the time interval between two consecutive phase IIIs in the duodenum. The progression velocity of phase III was calculated by determining the time interval for a phase III to migrate from the duodenum to the terminal ileum. The data were analyzed statistically by means of the student two-tailed test. Determination of dose dependency was made by linear regression analysis. In the text, averaged values are given as mean $\pm$ 1SD.

8.3. RESULTS

The frequency of slow waves with superimposed bursts of spikes in all recording sites increased from phase I of the MMC to reach the maximum in phase III, then it decreased rapidly during phase IV to start a new MMC cycle. The frequency of slow waves with superimposed spike potentials in the antrum, duodenum, and sphincter of Oddi for each control MMC phase in the duodenum is shown in Table 1.

Continuous infusion of 16,16-dm PGE₂ caused a reduction of the duration of the MMC cycle and an increase of the velocity of phase III migration from the duodenum to the

TABLE 1

Myoelectrical Activity of the Antrum, Duodenum, and Sphincter of Oddi

Bursts of Spikes/Min	Myoelectric Migrating Complex (MMC) Phase			
	I	II	III	IV
<u>Control MMC</u>				
Antrum	0	1.9 ± 0.2	3.0 ± 0.2	1.2 ± 0.3
Duodenum	0	6.2 ± 0.7	17.1 ± 0.7	4.6 ± 0.9
Sphincter of Oddi	2.6 ± 0.6	4.7 ± 0.6	5.3 ± 0.7	3.0 ± 0.6
Duration (min) [†]	52.3 ± 9.0*	26.9 ± 5.2*	7.5 ± 0.5	4.0 ± 0.4
<u>MMC During Infusion of 16,16-dm PGE₂ at 2 µg/kg/h</u>				
Antrum	0	2.0 ± 0.3	3.0 ± 0.2	1.5 ± 0.4
Duodenum	0	6.6 ± 0.8	16.6 ± 0.8	5.1 ± 0.8
Sphincter of Oddi	2.8 ± 0.6	4.8 ± 0.5	5.6 ± 0.6	2.9 ± 0.5
Duration (min) [†]	14.9 ± 3.2	13.9 ± 3.0	7.2 ± 0.4	3.8 ± 0.4

[†] Duration of each phase in the duodenum.

* This value is significantly greater than the corresponding value in the same column below at the 1% level, $p < 0.01$.

terminal ileum (Figure 1). These changes were dose-dependent (Table 2). The duration of the MMC cycle varied from 74.2 ± 11.4 min during infusion of 16,16-dm PGE₂ at 0.1 $\mu\text{g/kg/h}$ to 37.6 ± 6.4 min at 5.0 $\mu\text{g/kg/h}$ (correlation coefficient = 0.77; $p < 0.01$). The time interval for phase III to migrate from the duodenum to the terminal ileum varied from 64.4 ± 12.7 during infusion of 16,16-dm PGE₂ at 0.1 $\mu\text{g/kg/h}$ to 34.7 ± 6.0 at 5.0 $\mu\text{g/kg/h}$ (correlation coefficient = 0.69; $p < 0.01$).

The frequencies of slow waves with bursts of spikes in the antrum, duodenum, and sphincter of Oddi during infusion of 16,16-dm PGE₂ at 2 $\mu\text{g/kg/h}$ is shown in Table 1 and they were not significantly different from those of the control MMC phases. The time reduction of the MMC cycle was due to a shortening of the duration of both phase I and II. Phase III, observed during infusion of 16,16-dm PGE₂, was similar to that of the control MMC in duration (6 to 8 min), amplitude (7 to 10 mV), and frequency of bursts of spike potentials (17/min in the duodenum). There was no difference in the frequency of phase III migration to the terminal ileum between the control MMCs (89%) and during infusion of 16,16-dm PGE₂ (93%).

The duration of the next MMC cycle following administration of 16,16-dm PGE₂ at 1.0 (69.5 ± 12.3 min), 2.0 (67.4 ± 5.4 min), and 5.0 $\mu\text{g/kg/h}$ (56.0 ± 10.1 min) was significantly smaller than that of the control MMC (90.7 ± 15.0 min). There was no significant difference between the

Figure 1. Histograms of sphincter of Oddi and gastrointestinal tract myoelectric activity in a fasted opossum. Electrodes are positioned in the gastric antrum (A), sphincter of Oddi (SO), duodenum (D), distal jejunum (J), and distal ileum (I). Infusion of 16,16-dimethyl prostaglandin E₂ at a dose of 2 µg/kg/h reduced the duration of the MMC cycle and increased the velocity of propagation of phase III from the stomach to the ileum.

TABLE 2

Migrating Myoelectric Complex Cycle Duration and Velocity
of Propagation of Phase III During Infusion
of 16,16-Dimethyl Prostaglandin E₂

Dose of Prostaglandin ($\mu\text{g/kg/h}$)	MMC Duration (min)	Velocity of Propagation (min)
0.1	74.2 ± 11.4	64.4 ± 12.7
1.0	56.0 ± 10.1	49.2 ± 8.8
2.0	47.0 ± 4.3	39.8 ± 4.9
5.0	37.6 ± 6.4	34.7 ± 6.0
Control	90.7 ± 15.0	79.3 ± 15.0

duration of the control MMC cycle and that following infusion of 16,16-dm PGE₂ at 0.1 µg/kg/h (91.5 ± 15.6 min).

Bolus infusion of 16,16-dm PGE₂ at 2 µg/kg caused intense spike activity for two to four minutes in all recording sites simultaneously. The frequency of slow waves with bursts of spikes was 2 bursts of spikes/min in the antrum, 8 bursts of spikes/min in the sphincter of Oddi, 17 bursts of spikes/min in the duodenum, 15 bursts of spikes/min in the distal jejunum, and 14 bursts of spikes/min in the terminal ileum. The phase III continued its migration down to the terminal ileum but at a higher velocity. The time interval for phase III to migrate from the duodenum to the terminal ileum was 37.4 ± 4.7 min.

Diarrhea was observed in eight experiments, six following infusion of 16,16-dm PGE₂ at .5 µg/kg/h and two after infusion at 2 µg/kg/h. Diarrhea was defined as any bowel movement of liquid content that occurred during or within two hours of the experiment. There was no significant difference in MMC cycle duration between the MMC following indomethacin administration (84.2 ± 12.3 min) and control MMCs (90.0 ± 11.0 min).

8.4. DISCUSSION

Prostaglandins have been implicated as a possible cause of diarrhea in several clinical situations, including bacterial infections, colonic and thyroid cancers, irritable colon syndrome, food intolerance, and following radiotherapy

(11,12). Diarrhea has been observed following administration of prostaglandin E (2,6,13). The mechanism of diarrhea associated with prostaglandins is still not clear. Changes in gastrointestinal motility as well as water and electrolytic intestinal transport have been suggested as the cause of prostaglandin-induced diarrhea (2,6,7).

In the present study, we evaluate the effect of a methylated synthetic prostaglandin E_2 , 16,16-dimethyl prostaglandin, on the electromyographic activity of the gastrointestinal tract of the opossum. This animal exhibits gut myoelectric activity similar to that of humans and it usually lies quietly for many hours without the need of restraints, sedatives, or anesthetics. Continuous administration of 16,16-dm PGE_2 produced a dose-dependent increase in the frequency of MMCs and in the velocity of propagation of phase III from the duodenum to the terminal ileum. Since the activity front of each MMC (phase III) is associated with peristaltic contractions of the small bowel whose function is propulsion of gastrointestinal contents, an increase in the frequency and velocity of propagation of phase III may increase the delivery of gut contents into the colon and so contribute to diarrhea.

Mathias et al. reported that infusion of prostaglandin F_2 alpha into rabbit ileal loops produced a highly organized myoelectric pattern defined as migrating action potential complex. This myoelectric pattern was similar to that observed in animals that developed diarrhea secondary to

administration of cholera toxin (14).

Ruwart et al. observed an increase in the small intestine transit of a radioisotopic marker following intravenous administration of 16,16-dm PGE₂ in rats (15). An increase in ileal flow of a nonabsorbable marker during administration of both prostaglandin E₂ and F₂ was also reported by Milton-Thompson et al. in man (7). However, Konturek reported a prolongation of the MMC cycle duration following continuous intravenous infusion of prostaglandin E₂ in dogs (5). These different results may be related to the use of different animal species.

Prostaglandin E₂ has also been demonstrated to stimulate the motility of the isolated human stomach (12). The gastric emptying rate of test meal marker is increased following administration of 16,16-dm PGE₂ (3). In our study, a bolus administration of high doses of 16,16-dm PGE₂ interrupted the MMC temporarily and increased the spike activity of the antrum of the stomach as well as of the small bowel and sphincter of Oddi. Continuous infusion of 16,16-dm PGE₂ also increased the motility of the antrum, but in an organized fashion. In this situation, the increase in spike activity of the antrum was associated with a precocious appearance of phase III of the MMC in the upper gastrointestinal tract, which migrated distally to the terminal ileum at a higher velocity than in the control MMCs.

The physiologic role of prostaglandins in modulating

the motility of the gastrointestinal tract is controversial (16). The observations that prostaglandin E_2 is produced in the intestine and that administration of prostaglandins and inhibitors of prostaglandin synthesis change gastrointestinal motility suggest that endogenous prostaglandin synthesis may have a role in regulating intestinal motility (15,17,18). Several authors have reported an increase in the motility of the gastrointestinal tract following administration of prostaglandin inhibitors both in vivo and in vitro (19,20). However, other authors observed a decrease in activity of the small intestine in guinea-pig ileum and human small intestine following administration of aspirin and indomethacin (5,18). Borowska et al. reported that application of aspirin, indomethacin and suprofen to the intestinal serosa did not affect peristalsis in the small intestine of the mouse (21). We have observed no change in either the electromyographic activity of the antrum, small bowel, or sphincter of Oddi of the fasted opossum following intravenous administration of indomethacin. This finding does not eliminate the possibility that prostaglandin may have a role in regulating the gastrointestinal tract motility.

Honda et al. and our group have demonstrated that although the myoelectric activity of the sphincter of Oddi is independent from that of the duodenum, the frequency of bursts of spike potentials in the sphincter of Oddi correlates with the MMC phases in the duodenum (9,10).

Continuous infusion of 16,16-dm PGE₂ did not terminate the correlation between the spike activity of the sphincter of Oddi with the shortened MMC phases of the duodenum.

It is concluded from this study that continuous infusion of 16,16-dm PGE₂ increases the frequency of MMCs and the velocity of propagation of the activity front of the MMC from the antrum to the terminal ileum in the opossum. These changes in gastrointestinal motility may be important contributory factors in the etiopathogenesis of prostaglandin-induced diarrhea.

8.5.SUMMARY

Myoelectric recordings of the opossum gastrointestinal tract were performed during continuous infusion of 16,16-dimethyl prostaglandin E₂ at 0.1, 1, 2 and 5 µg/kg/h. Prostaglandin causes a dose-dependent reduction of the duration of the MMC cycle and an increase in the velocity of phase III migration from the duodenum to the terminal ileum. The time reduction of the MMC cycle was due to a shortening of the duration of both phase I and II. Bolus infusion of 16,16-dimethyl prostaglandin caused intense spike activity for two to four minutes in all recording sites simultaneously. Administration of indomethacin did not change the myoelectric activity of the gastrointestinal tract. Diarrhea was observed in eight experiments. These changes in gastrointestinal motility may be important contributory factors in the etiopathogenesis of

prostaglandin-induced diarrhea.

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CHAPTER 9

SEROTONIN INCREASES THE VELOCITY OF PROPAGATION AND FREQUENCY OF THE MIGRATING MYOELECTRIC COMPLEXES

9.1. INTRODUCTION

The main source of 5-hydroxytryptamine (serotonin) in mammals, including humans, is the enterochromaffin cells and enterochromaffin-like cells in the gastrointestinal tract (1). The physiological role of this amine in the motility of the gastrointestinal tract is still controversial (1,2). It has been suggested that the elevated production of serotonin by carcinoid tumors is responsible for the increased motility of the intestine and the diarrhea observed in this condition (3,4).

The most common techniques employed to evaluate the effect of serotonin on gastrointestinal tract motility have been determinations of contractions of muscle strips in vitro, intraluminal pressures, extraluminal contractile forces, and movements of radiopaque substances (5-9). Recent developments in electromyography have allowed a more detailed evaluation of the gastrointestinal tract motility. Several animals, including man, opossum, and dog exhibit a characteristic fasting motility pattern of the gastrointestinal tract that has been termed the migrating

myoelectric complex (MMC) which periodically propagates down the digestive tract from the stomach to the terminal ileum (10,11). Ruckebusch and Bardon have evaluated the effect of bolus administration of serotonin on the MMC in the stomach and duodenum of sheep (12). Our objective in the present study is to assess the effect of both continuous and bolus administration of serotonin on the myoelectric activity of the gastrointestinal tract and sphincter of Oddi of the opossum.

9.2. MATERIAL AND METHODS

Under sodium pentobarbital anesthesia that was administered intraperitoneally at a dose of 25 mg/kg, seven fasted opossums were subjected to an upper midline laparotomy.

Bipolar electrodes of silver-plated copper wires of 36 AWG size were implanted in the muscular layer of the sphincter of Oddi and gastrointestinal tract through a 25 gauge hypodermic needle. The wire was loosely tied off and the free end was trimmed. A total of seven pairs of electrodes were placed, one in the sphincter of Oddi, one in the distal antrum, one in the duodenum (two centimeters distal to the sphincter of Oddi-duodenal junction), and four at equidistant intervals from the proximal jejunum to the distal ileum.

A silastic catheter was placed into the jugular vein. The catheter and the wires were brought subcutaneously to the interscapular region. The wires were previously soldered to a female socket. The socket and the catheter were attached to the skin.

Experiments were started seven to ten days after the operation. The animals were fasted for 12 to 15 hours before each study. Myoelectric activity was recorded on an eight-channel Gould 2800S instrument (Gould, Inc., Recording Systems Division, Cleveland, Ohio) using a paper speed of 1 mm/s, low frequency cut-off filter of 1 Hz, high frequency cut-off filter of 10 Hz, and an overall sensitivity of 25 or 50 mV. A male socket connected to the recording instrument was plugged into the opossum's back socket for each recording session. No anesthetics or sedatives were administered to the animals.

After one to three spontaneously occurring MMCs had been recorded, 0.01, 0.1, 0.2, 0.5, or 1.0 mg/kg/h of serotonin creatinine sulfate (Sigma Chemical Co., St. Louis, Missouri) was administered intravenously at a continuous rate of 0.2 ml/min employing a Harvard pump. A total of ten studies was obtained for each dose. The infusion was started at the beginning of phase I of the MMC in the duodenum and was continued for the time period of one MMC cycle. Finally, the next MMC following termination of the serotonin infusion was also recorded.

In additional experiments, bolus intravenous infusions

of methysergide maleate (Batch 78001, Sandoz Pharmaceuticals, East Hanover, New Jersey) at a dose of 1 mg/kg were given alone (ten studies) at the beginning of phase I of the MMC in the duodenum or preceding infusion of serotonin at 1 mg/kg/h (ten studies).

Finally, bolus infusion of serotonin at 0.2 mg/kg was also performed at the beginning of phase I of the MMC in the duodenum in ten other studies.

The different phases of the MMC were identified using the criteria of Code and Marlett (11). The progression velocity of phase III was calculated by determining the time interval for a phase III to migrate from the duodenum to the terminal ileum. The recordings were divided into two-minute intervals and the average frequency of slow waves with superimposed spike potentials for each phase of the MMC was determined. The data were analyzed statistically by means of the student two-tailed test. Determination of dose dependency was made by linear regression analysis. The average MMC cycle duration was plotted against the logarithmic serotonin concentration. In the text, averaged values are given as mean $\pm$ 1 SD.

9.3. RESULTS

Slow waves occurred at a rate of 3.3/min. in the antrum, 18/min in the duodenum and sphincter of Oddi, and 15/min in the terminal ileum. The average duration of the MMC in the dudodenum was 93.7 ± 15.8 min and the time

interval for a phase III to migrate from the duodenum to the terminal ileum was 84.3 ± 12.6 min.

Honda et al. and our group have demonstrated previously that, although the frequency of spike potentials is different in the sphincter of Oddi and duodenum, there is a temporal correlation between the MMC phases in the sphincter of Oddi and duodenum (13,14). All phases in the sphincter of Oddi started almost simultaneously with the MMC phases in the proximal duodenum. Therefore, the myoelectric activity of the sphincter of Oddi was also divided into four phases.

Continuous infusion of serotonin reduced the periodicity of the MMC. The MMC cycle duration reduction was dose-dependent (correlation coefficient = 0.82; $p < 0.01$) and the cycle length varied from 90.6 ± 15.6 min. during infusion of serotonin at 0.01 mg/kg/h to 36.6 ± 5.4 min. during infusion at 1.0 mg/kg/h (Figure 1). There was no difference in the MMC cycle duration between the control group (93.7 ± 15.8 min) and during infusion of serotonin at 0.01 mg/kg/h (90.6 ± 15.6 min).

The reduction of the MMC cycle duration was the result of the decrease in time of both phases I and II. Phase III obtained during administration of serotonin was similar to the control phase III in duration (6-8 min), frequency of spike activity (18 spikes/min in the duodenum), and amplitude of the spike potentials (10-14 mV). In addition, the frequency of phase III migration to the terminal ileum during administration of serotonin (86%) was similar to that

Figure 1. Dose-response relationship of intravenous infusion of serotonin on the MMC cycle duration.

of the control MMC (91%). As in the control group, when phase III was seen in the terminal ileum, a new one was beginning in the duodenum. The time required for a phase III to migrate from the duodenum to the terminal ileum during administration of serotonin at 1 mg/kg/h was 35.8 ± 5.5 min (Figure 2).

The average frequency of slow waves with spike potentials in the sphincter of Oddi, antrum, and duodenum for each phase of the MMC during the administration of serotonin at 1 mg/kg/h is shown in Table 1. There was no significant difference as compared to the MMC preceding the administration of serotonin. The duration of the MMC following serotonin infusion was similar to the control, except when the infusion dose was 1 mg/kg/h. At this dose, the MMC following serotonin infusion (76.2 ± 12.1 min) was shorter than the control (90.1 ± 12.9 min) ($p < 0.05$).

Bolus administration of serotonin at 0.2 mg/kg caused the appearance of intense spike activity simultaneously in all recording sites for a period of 3-5 min. The frequency of bursts of spike potentials was 2 spikes/min in the antrum, 7 spikes/min in the sphincter of Oddi, 17 spikes/min in the duodenum, and 14 spikes/min in the ileum.

The cycle duration of the two MMCs following administration of methysergide was similar to that of the control MMCs. After administration of methysergide, infusion of serotonin at 1.0 mg/kg/h reduced the cycle duration of the MMC to only 71.0 ± 15.3 min. This value was

Figure 2. Histograms showing temporal distribution of slow waves with spike potentials in the antrum (A), sphincter of Oddi (SO), duodenum (D), distal jejunum (J), and distal ileum (I) of an opossum. Infusion of serotonin at a dose of 1 mg/kg/h reduced the duration of the MMC cycle and increased the velocity of propagation of phase III from the stomach to the ileum.

TABLE 1

Myoelectrical Activity of the Antrum, Duodenum, and Sphincter of Oddi

Bursts of Spikes/Min	Myoelectric Migrating Complex (MMC) Phase			
	I	II	III	IV
<u>Control MMC†</u>				
Antrum	0	1.9 ± 0.3	3.1 ± 0.2	1.8 ± 0.2
Duodenum	0	5.9 ± 0.8	16.7 ± 0.7	5.3 ± 0.8
Sphincter of Oddi	2.8 ± 0.5	4.3 ± 0.4	5.7 ± 0.4	3.2 ± 0.5
Duration (min)††	50.1 ± 8.2	31.3 ± 5.4	6.7 ± 0.4	4.1 ± 0.6
<u>MMC During Infusion of Serotonin at 1 mg/kg/h†</u>				
Antrum	0	2.1 ± 0.3	3.1 ± 0.3	2.0 ± 0.3
Duodenum	0	6.5 ± 0.7	16.5 ± 0.5	4.9 ± 0.3
Sphincter of Oddi	3.0 ± 0.2	4.7 ± 0.4	6.1 ± 0.3	3.0 ± 0.4
Duration (min)††	12.3 ± 2.9*	14.5 ± 3.5*	6.2 ± 0.4	3.6 ± 0.5

† Values given as mean ± 1 S.D.

†† Duration of each phase in the duodenum.

* This value is significantly greater than the corresponding value in the column above at the 1% level, $p < 0.01$.

significantly greater than the MMC duration obtained during infusion of serotonin at 1 mg/kg/h with no prior administration of methysergide (36.6 ± 5.4 min; $p < 0.01$).

Diarrhea was observed in four experiments, three in which serotonin was infused at a dose of 1 mg/kg/h and one experiment at a dose of 0.5 mg/kg/h. Diarrhea was defined as any bowel movement of liquid content that occurred during or within two hours of the experiment.

9.4. DISCUSSION

We have employed electromyography to evaluate the effect of 5-hydroxytryptamine on the motility of the gastrointestinal tract. This technique allows one to assess the effects of a substance in animals in vivo for prolonged periods of time and without the use of sedatives or anesthetics. In addition, the opossum provides important advantages. This animal usually lies quietly for many hours without the need of restraints and it exhibits a myoelectric activity of the gastrointestinal tract similar to man. The sphincter of Oddi in this species is extraduodenal and measures 2-3 cm in length and, therefore, dissection of the pancreas and duodenum is not necessary in order to implant the electrodes.

In our study, continuous intravenous administration of serotonin reduced the cycle duration of the MMC and increased the velocity of propagation of the phase III. These changes were dose-dependent and were observed only

with high doses of serotonin of 0.1 mg/kg/h or more. Infusion at 0.01 mg/kg/h had no effect on the motility of the gastrointestinal tract. The changes observed in the motility of the gastrointestinal tract were not more intense in some specific segments of the small bowel as suggested by some authors (17). The changes occurred in all segments of the gastrointestinal tract studied, included the antrum, and were characterized by a continuous and organized increase in the velocity of propagation of the activity front (phase III) of the MMC from the antrum to the terminal ileum.

Bolus infusion of 5-hydroxytryptamine interrupted the MMC temporarily and increased the spike activity of the gastrointestinal tract in all recording sites simultaneously. This effect was temporary, possibly due to rapid metabolism of serotonin, primarily in the liver and lungs. Ruckebusch and Bardon also described a simultaneous increase in the contractile activity of the antrum and duodenum following intravenous bolus administration of serotonin in sheep (12). Recordings of the jejunum and ileum were not obtained in their study. On the other hand, these authors observed that intravenous administration of methysergide, at a dose of 0.1 mg/kg, increased the MMC frequency in the antrum and duodenum. The cycle reduction was less prominent following intraduodenal than intravenous infusion of methysergide. We have observed no change of MMC cycle duration following intravenous administration of methysergide. These different results may be related to the

use of different animal species.

However, evidence has accumulated recently that serotonin stimulates the intestine by acting on receptors on cholinergic neurons and directly on smooth muscle receptors (18). Methysergide is an effective, competitive antagonist of 5-hydroxytryptamine on smooth muscle serotonin receptors but not on serotonin receptors on cholinergic neurons of the small intestine (18,19). Therefore, the partial inhibition of the effect of serotonin on the MMC cycle duration by methysergide observed in our study is possibly due to the selective inhibition of methysergide at the smooth muscle receptors but not at the neuroenteric receptors.

Serotonin has been demonstrated to stimulate the motility of the stomach and small bowel both in vivo and in vitro in several species including man, dog, cat, and mouse (5-9,15). Administration of large doses of 5-hydroxytryptamine induces diarrhea in mice and other animals (16). In man, the increased production of serotonin by carcinoid tumors has been associated with hypermotility of the small bowel and diarrhea (3). Antiserotonergic agents may control or alleviate these annoying symptoms in patients with carcinoid tumors.

The mechanism by which serotonin-producing tumors cause diarrhea is not clear. This study suggests that an increase in the velocity of propagation and frequency of the MMC may play an important role in the production of diarrhea in patients with carcinoid syndrome. A comparable pattern of

organized myoelectric activity was observed during experimental studies with toxins and bacteria cultures. Mathias et al. found that infusion of cholera enterotoxin to rabbits induced a series of organized migrating action potentials complexes in an ileal loop (20). Similar abnormal patterns of small bowel motility were observed following administration of other agents which induce diarrhea (21,22).

The change in frequency of spike potentials in the sphincter of Oddi during infusion of serotonin also correlates with the MMC in the duodenum. There was a proportional reduction of the duration of the MMC phases in the sphincter of Oddi, but the frequency for each phase, prior to and during infusion of serotonin, was similar.

We concluded from this study that continuous infusion of serotonin in the opossum increases the frequency of MMCs and the velocity of propagation of phase III of the MMC from the antrum to the terminal ileum. This change in the motility of the gastrointestinal tract may be responsible for the diarrhea associated with administration or increased synthesis of serotonin by carcinoid tumors.

9.5. SUMMARY

The effect of serotonin on the myoelectric activity of the gastrointestinal tract was evaluated in seven opossums. The following doses of serotonin were administered intravenously at a continuous rate of 0.2 ml/min: 0.01, 0.1,

0.2, 0.5, and 1.0 mg/kg/h. Serotonin reduced the periodicity of the migrating myoelectric complexes. The migrating myoelectric complex cycle duration reduction was dose-dependent (correlation coefficient = 0.82; $p < 0.01$) and the cycle length varied from 90.6 ± 15.6 minutes during infusion of serotonin at 0.01 mg/kg/h to 36.6 ± 5.4 minutes during infusion at 1.0 mg/kg/h. The time interval for a phase III to migrate from the duodenum to the terminal ileum during administration of serotonin at 1.0 mg/kg/h was 35.8 ± 5.5 minutes (control 84.3 ± 12.6 minutes; $p < 0.01$). The cycle duration of the two migrating myoelectric complexes following administration of methysergide at 1.0 mg/kg was similar to the control migrating myoelectric complexes. Diarrhea was observed in four experiments. We concluded that continuous infusion of serotonin in the opossum increases the velocity of propagation of the phase III of the migrating myoelectric complex from the antrum to the terminal ileum.

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CHAPTER 10

GENERAL DISCUSSION

The role of the sphincter of Oddi in transporting biliopancreatic secretion into the duodenum and as a source of upper abdominal pain, jaundice, and pancreatitis has been controversial. Initial studies suggested that the transport of bile into the duodenum was dependent only on the rate of pressure of hepatic bile production, the gallbladder contraction, and the resistance of the sphincter of Oddi. These studies suggested that the sphincter of Oddi remained closed during fasting and that, following a meal, the sphincter relaxed and allowed bile to flow into the duodenum. However, recent studies employing electromyography, cineradiography, and endoscopic manometric techniques indicate that this simple concept of motor activity of the sphincter of Oddi is not accurate. The sphincter of Oddi actually has a more active role. It probably propels pancreatic juice and bile into the duodenum by a milking mechanism and has a major function of coordinating the time and rate of draining these secretions into the duodenum.

Endoscopic continuous pressure recordings of the pancreatic

and biliary ducts and sphincters in man have shown that the motility of the sphincter of oddi is different from that of the duodenum and that the sphincter of Oddi exhibits phasic wave activity that usually migrates in an antegrade fashion. The determination of the frequency and amplitude of these phasic waves as well as the basal sphincter of Oddi pressure has become important clinically in order to recognize patients with biliary dyskinesia. Phasic waves and pressure changes in the sphincter of Oddi following administration of morphine and cholecystokinin may also be of diagnostic value.

Electromyography has emerged as an important experimental tool used to study the motility of the gastrointestinal tract. Recently, electromyography of the sphincter of Oddi has also been performed in the rabbit and the opossum. This method allows one to evaluate the effect of several drugs on conscious, nonanesthetized animals over prolonged periods of time. Simultaneous biliary and pancreatic pressure recordings may provide additional information. In the present thesis, electromyography of the gastrointestinal tract and sphincter of Oddi in the opossum was evaluated in eight experimental studies. Initially, the experiments were performed under physiological conditions in nonmedicated, conscious animals, both in the fasting and fed states. The effect of gastrointestinal hormones that possibly influence the digestive process was assessed. Motility of the gastrointestinal tract and sphincter of Oddi following abdominal operations and administration of substances that cause gastrointestinal disturbances was also studied.

The normal electromyographic pattern of the sphincter of Oddi and gastrointestinal tract was described in Chapter 2. The sphincter of Oddi in the Opossum generated spontaneous spike potentials which propagated from the proximal to the distal portion of the sphincter. The spike potentials are associated with peristaltic contractions of the sphincter of Oddi which possibly have the function of transporting bile and pancreatic juice from the sphincter of Oddi into the duodenum. This hypothesis has been confirmed by combined electromyographic and cineradiographic studies.

Although the spike activity in the sphincter of Oddi was different from that in the duodenum, the frequency of spike potentials in the sphincter of Oddi correlated with the myoelectric migrating complex (MMC) phases in the duodenum. The frequency of sphincter of Oddi spike potentials increased from phase I to phase II of the MMC and then it decreased rapidly during phase IV to start a new cycle.

A new experimental model which allowed correlation of pancreatic duct and common duct pressure with the motility of the sphincter of Oddi was also described. A temporary elevation of the pancreatic and biliary duct pressures of 1 to 3 mmHg was observed with each sphincter of Oddi spike potential in most experiments. There was a variation in the number of pressure elevations related to the frequency of spike potentials in the sphincter of Oddi during feeding and the four phases of the MMC, but baseline pressure remained constant. The constant baseline pancreatic and biliary duct pressures during all MMC phases and

feeding state suggest that pressure is not the main regulatory mechanism of bile and pancreatic juice flow into the duodenum. It is possible that the spike potential variation in the sphincter of Oddi may have an important role in the rate of biliopancreatic secretion into the duodenum.

In Chapter 3, electromyographic recordings were obtained from conscious opossums both in the fasted state and following administration of isocaloric amounts of protein, fat, carbohydrate, and a mixture of equal parts of these three nutrients. A correlation between the frequency of spike potentials in the sphincter of Oddi and the small bowel was observed. The aliments that caused more spike activity in the small bowel were the same ones that increased the frequency of spike potentials in the sphincter of Oddi.

Fat and mixed food resulted in the greatest incidence of spike activity in the gastrointestinal tract, followed by protein. The lowest incidence of slow waves with spike potentials in the small bowel was observed following feeding of carbohydrates. The lowest spike activity in the sphincter of oddi was observed after carbohydrate feeding. There was no significant difference in the incidence of spike potentials in the sphincter of Oddi following administration of fat, protein, and mixed food. The duration of the fed pattern was related to the type of food; fat caused the longest duration and the shortest fed pattern was created by ingestion of carbohydrate. A correlation between the duration of the fed pattern and the frequency of spike potentials in the sphincter of Oddi and gastrointestinal tract was also

observed.

In Chapter 4, electromyographic activities of the sphincter of Oddi and duodenum and the pancreatic and biliary duct pressures were recorded during continuous infusion of cholecystokinin, pentagastrin, glucagon, secretin, and acetylcholine. Cholecystokinin and pentagastrin increased the frequency of spike potentials in the sphincter of Oddi and duodenum and, in most instances, interrupted the MMC. The new myoelectric activity pattern resembled that of the fed state. Glucagon and secretin inhibited the onset of the MMC and reduced the frequency of slow waves with superimposed spike potentials in the sphincter of Oddi and duodenum. Although there was variation in the frequency of pressure elevations related to sphincter of Oddi spike potentials, the baseline pressure in the common duct and pancreatic duct remained constant during infusion of the hormones.

Acetylcholine was the substance that caused the greatest increase in the frequency of bursts of spike potentials into the sphincter of Oddi and duodenum; almost each slow wave in the sphincter of Oddi and duodenum was superimposed with spike potentials. This intense spike activity in the sphincter of Oddi possibly hampered bile and pancreatic juice refilling of the sphincter and transport into the duodenum. Therefore, both biliary and pancreatic duct pressures increased.

The findings of this study suggest that the pancreatic and biliary duct pressures are maintained at a constant level by increasing or decreasing the flow of biliopancreatic secretion

into the duodenum through changes in the frequency of sphincter of Oddi spike potential. The gastrointestinal hormones may have an important role in regulating the excretion of bile and pancreatic juice into the duodenum.

In Chapter 5, the effect of abdominal operations on the sphincter of Oddi and gastrointestinal myoelectric activity was evaluated both in the fasting and fed states. Five different surgical procedures were performed: a five-minute, a one-hour, and a three-hour laparotomy with intestinal handling, enteroenterostomy, and gastrojejunostomy.

Although the time of appearance of the MMC following the abdominal operations varied with the type and duration of the surgical procedures, normal myoelectric activity of the gastrointestinal tract was observed within 24 hours after the operations in most experiments. Procedures that severed the upper gastrointestinal tract interrupted the MMC for longer periods of time. The time of appearance of the MMC was proportional to the duration of the operation.

Administration of food on the first day that the MMC was observed after the operation resulted in a normal fed pattern in all but two experiments, one of which occurred in an animal with an intra-abdominal abscess. A fed pattern did not occur when food was infused before the MMC appearance. These findings suggest that the presence of the MMC is necessary to have a normal fed pattern. However, the fed pattern may be absent or delayed in animals that have a normal MMC, as in the instance of the opossum with an intra-abdominal abscess. The results from this study

support the view that intestinal motility is not depressed for prolonged periods of time following most abdominal operations.

In Chapter 6, recordings of the electromyographic activity of the sphincter of Oddi and upper gastrointestinal tract and pancreatic and biliary duct pressures were obtained during administration of ethanol into the stomach or into the duodenum. Instillation of alcohol caused a minute burst of spike activity in the duodenum that was followed by a five- to ten-minute quiescent period. A vigorous phase III-like activity then ensued in most experiments. This phase III-like activity was similar to the normal MMC phase III in duration, frequency, and amplitude of spike potentials.

A significant increase in the frequency of spike potentials occurred for 15 to 20 minutes in the sphincter of Oddi in all experiments. The two largest increases occurred in the first minute after alcohol instillation and simultaneous with phase III-like activity in the duodenum. There was an increase in the number of pancreatic and biliary pressure elevations related to sphincter of Oddi spike-burst potentials following ethanol instillation, but baseline pressures remained constant.

Repetitive myoelectric activity disturbances of the sphincter of Oddi that may occur following chronic ingestion of alcohol may be an important contributory factor in the pathogenesis of alcoholic pancreatitis.

The mechanism by which alcohol stimulates the motility of the sphincter of Oddi and duodenum was evaluated in Chapter 7. Ethanol was infused into the stomach, duodenal stump, jejunum,

and intravenously in opossums that were subjected to gastrojejunostomy with duodenal exclusion. The concentration of plasma motilin was also determined during the normal MMC phases and during the phase III-like activity caused by alcohol.

Instillation of ethanol into the stomach or duodenum caused phase III-like activity in the sphincter of Oddi and upper gastrointestinal tract in most experiments. Jejunum or intravenous infusion of ethanol did not change the motility of the sphincter of Oddi. There was no correlation between alcohol blood levels and the appearance of phase III-like activity.

The concentration of plasma motilin was elevated during phase III-like activity caused by ethanol and was similar to that of the normal phase III of the MMC. This suggests that the phase III-like activity produced by administration of alcohol may be caused by the release of motilin from the upper gastrointestinal tract.

In Chapter 8, the electromyographic pattern of the gastrointestinal tract and sphincter of Oddi was evaluated during infusion of 16,16 dimethyl prostaglandin E_2 (dmpGE₂). Instillation of dmpGE₂ increased the velocity of propagation of the MMC in the gastrointestinal tract from the stomach to the terminal ileum. A reduction of the duration of the MMC was also observed. The time reduction of the MMC was due to a shortening of the duration of both phases I and II. Phase III was similar to the control in duration, amplitude, and frequency of bursts of spike potentials. The reduction of the MMC was dose-dependent and varied from 37.6 ± 6.4 minutes during infusion of dmpGE₂ at 5

$\mu\text{g/kg/h}$ to 74.2 ± 11.4 minutes at $0.1 \mu\text{g/kg/h}$. Bolus infusion of dmPGE_2 caused intense spike activity for two to four minutes in all recording sites. Administration of indomethacin did not change the myoelectric activity pattern of the sphincter of Oddi and duodenum.

These important changes in the gastrointestinal motility may be responsible for the diarrhea that is often observed following administration of dmPGE_2 during experimental treatment of peptic ulcer disease.

The effect of both continuous and bolus administration of serotonin on the myoelectric activity of the gastrointestinal tract and sphincter of Oddi was assessed in Chapter 9. Continuous intravenous administration of serotonin increased the velocity of propagation of the phase III and reduced the duration of the MMC. These changes were dose-dependent and were observed only with high doses of serotonin of 0.1 mg/kg/h or more. The changes occurred in all segments of the gastrointestinal tract studied and were characterized by organized increase in the velocity of propagation of the activity front of the MMC from the antrum to the terminal ileum.

Bolus infusion of serotonin interrupted the MMC temporarily and increased the frequency of spike potential in all recording sites of the gastrointestinal tract simultaneously.

Infusion of methysergide did not change the cycle duration of the MMC. However, administration of methysergide prior to infusion of serotonin partially inhibited the effects of serotonin on the MMC cycle duration.

This partial inhibition is possibly due to the selective inhibition of methysergide on the smooth muscle receptors but not in the neuroenteric receptors.

The change in frequency of spike potentials in the sphincter of Oddi during infusion of serotonin also correlated with the MMC in the duodenum. This study suggests that an increase in the velocity of propagation and frequency of the MMC may play an important role in the production of diarrhea in patients with carcinoid syndrome.

Several conclusions can be drawn from these experimental studies. Although the motility in the sphincter of Oddi is different from that in the duodenum, both the sphincter of Oddi and duodenum exhibit cyclic changes in the frequency of spike potentials that correlate with the phases of the MMC. The correlation between the frequency of spike potentials in the sphincter of Oddi and duodenum was observed during fasted and fed states and during administration of all substances evaluated in this series of experiments. The findings that cholecystokinin and pentagastrin stimulate and that glucagon and secretin decrease the frequency of burst of spikes in the sphincter of Oddi suggest that these gastrointestinal hormones may have an important function in controlling the flow of biliopancreatic secretion into the duodenum. The intense spike activity that occurred in the sphincter of Oddi following infusion of alcohol may contribute to sphincter of Oddi dysfunction. The increase in motilin plasma levels following administration of ethanol suggests that phase III-like activity produced by instillation of

alcohol may be caused by the release of motilin from the upper gastrointestinal tract. The increase in velocity of propagation of phase III of the MMC from the antrum to the terminal ileum during infusion of serotonin and 16,16 dimethyl prostaglandin E₂ may be an important contributory factor in the production of diarrhea in patients with carcinoid syndrome or following administration of these two substances. The return of normal gastrointestinal tract motility following abdominal operations depends on the type and duration of surgical procedure. Although intestinal motility is normal within 24 hours following most abdominal operations, procedures that severed the upper gastrointestinal tract caused the longest disruption of the intestinal motility.

The application of these conclusions to the clinical situation needs additional investigations. Other studies demonstrated that the myoelectric activity of the gastrointestinal tract of the man is similar to that of the opossum, both in the fasting and fed states. Endoscopic manometric studies have also showed that the human sphincter of Oddi also exhibits phasic wave contractions that migrates distally, suggesting, therefore, a pumping mechanism in the sphincter of Oddi, like in the opossum. Further studies are also necessary to evaluate the motility of the sphincter of Oddi following operations on the sphincter, i.e., sphincterotomy and sphincteroplasty.

SUMMARY

In order to study the motility of the gastrointestinal tract and sphincter of Oddi, the opossum was employed as an experimental animal. Electromyographic recordings of the gastrointestinal tract and sphincter of Oddi were performed in conscious, non-medicated opossums under physiologic conditions and following abdominal operations or administration of several substances. Although the spike activity in the sphincter of Oddi was different from that in the duodenum, its frequency correlated with the migrating myoelectric complex (MMC) phases in the duodenum. Temporary elevation of the pancreatic and biliary duct pressures was observed with each sphincter of Oddi spike potential in most experiments. There was a variation in the frequency of pressure elevations related to spike-burst potentials during the four phases of the MMC and feeding, but base-line pressures remained constant.

After feeding, the interdigestive phases of the MMC in the sphincter of Oddi and duodenum were abolished and substituted by a fed activity pattern. The frequency of spike potentials in the sphincter of Oddi and small bowel and the duration of the fed pattern were dependent on the type of food. They were the greatest for fat and mixed food, intermediate for protein, and the lowest for carbohydrate.

Administration of cholecystokinin and pentagastrin abolished the MMC and caused a fed pattern-like activity

in the sphincter of Oddi and duodenum. Glucagon and secretin reduced the frequency of spike potentials or inhibited the onset of the MMC. Acetylcholine was the substance that caused the greatest spike activity in the sphincter of Oddi and duodenum.

Normal myoelectric activity of the gastrointestinal tract was observed within 24 hours following most abdominal operations and its appearance depended on the type and duration of the surgical procedure. A fed pattern did not occur in the experiments in which food was given before the appearance of the MMC. However, a normal fed pattern was observed on the first day of the MMC appearance in all but two animals, one of which had an intra-abdominal abscess.

Instillation of alcohol into the stomach or duodenum caused appearance of intense spike activity in the sphincter of Oddi and duodenum that was similar to phase III of the MMC in duration, frequency, and amplitude of spike potentials. There was no correlation between appearance of phase III-like activity and alcohol blood level. The concentration of plasma motilin was elevated during phase III-like activity and was similar to that of the normal phase III of the MMC. This suggests that administration of alcohol causes phase III-like activity due to the release of motilin from the upper gastrointestinal tract.

Continuous intravenous infusion of 16,16 dimethyl prostaglandin E₂ and serotonin increases the frequency of MMC and the velocity of propagation of phase III of

the MMC from the antrum to the terminal ileum. The change in frequency of spike potentials in the sphincter of Oddi during infusion of 16,16 dimethyl prostaglandin E₂ and serotonin also correlates with the MMC in the duodenum. These changes in the motility of the gastrointestinal tract may be responsible for the diarrhea associated with administration of 16,16 dimethyl prostaglandin E₂ or increased synthesis of serotonin by carcinoid tumors.

It is concluded from these experimental studies that although the motility in the sphincter of Oddi is different from that in the duodenum, both the sphincter of Oddi and duodenum exhibit cyclic changes in the frequency of spike potentials that correlate with the phases of the MMC. The correlation between the frequency of spike potentials in the sphincter of Oddi and duodenum was observed during fasted and fed states and during administration of all substances evaluated in this series of experiments. Changes in the motility of the sphincter of Oddi following administration of different foods or gastrointestinal hormones may be important in controlling the flow of biliopancreatic secretion into the duodenum. Disturbances in the myoelectric activity of the sphincter of Oddi following infusion of alcohol may contribute to sphincter of Oddi dysfunction.

SAMENVATTING

Ter bestudering van de motiliteit van tractus digestivus in het algemeen en de sphincter van Oddi in het bijzonder worden in dit proefschrift de resultaten beschreven van electromyografische registratie van de tractus digestivus en de sphincter van Oddi. De experimenten en registraties werden verricht bij opossums onder fysiologische omstandigheden zonder medicatie na abdominale operaties en na toedienen van verschillende medicamenten. De actie potentialen in de sphincter van Oddi verschilden van die in het duodenum, maar de frequentie correleerde met de fasen van het migrerend motorisch complex (MMC) in het duodenum. Tijdens iedere actie potentiaal van de sphincter van Oddi werd in de meeste experimenten een tijdelijke verhoging van de druk in de ductus pancreaticus en de ductus choledochus gevonden. Er was een variatie in het aantal drukverhogingen die afhankelijk was van het patroon van het activiteitenfront van actie potentialen gedurende de vier verschillende fasen van het MMC en tijdens voeding, maar de basale drukken bleven onveranderd.

Na voeding verdween het normale fasen patroon van het MMC in de sphincter van Oddi en het duodenum. In plaats hiervan verscheen een voedings-activiteitspatroon. De frequentie van de actie potentialen in de sphincter van Oddi en in de dunne darm en de duur van het bij voeding passend

activiteitspatroon bleken afhankelijk te zijn van de aard van de voeding. Zij waren het grootst na vet en gemengd voedsel, iets minder na het toedienen van eiwitten, en het laagst na koolhydraten.

Toediening van cholecystokinine en pentagastrine gaven aanleiding tot afbraak van het MMC, zowel in de sphincter van Oddi als in het duodenum een activiteitspatroon passend bij voeding. Glucagon en secretine gaven een vermindering van het aantal actie potentialen of verhinderden het ontstaan van het MMC. Acetylcholine veroorzaakte de grootste elektrische activiteit in de sphincter van Oddi en het duodenum.

Na een laparotomie keerde de normale elektrische activiteit van de darm meestal weer binnen 24 uur terug. Dit was afhankelijk van het type en de duur van de operatie. Na toediening van voedsel verscheen het voedings-activiteitspatroon niet voordat het MMC was terug gekeerd.

Toediening van alcohol in maag en duodenum veroorzaakte een verhoging van elektrische activiteit en actie potentialen in de sphincter van Oddi en het duodenum, gelijk aan die van fase III van het MMC, in duur, frequentie en amplitude (van de potentialen). Er was geen correlatie tussen het verschijnen van deze activiteit en de alcohol spiegel in het bloed. De concentratie van het darmhormoon motiline in het plasma was verhoogd tijdens de op fase III gelijkende activiteit en was gelijk aan die tijdens een normale fase III van het MMC. Dit suggereert dat toedienen van

alcohol een op fase III gelijkende elektrische activiteit veroorzaakt, als gevolg van het vrijkomen van motiline in het bovenste deel van de tractus digestivus.

Continue intraveneus toedienen van 16,16 dimetyl prostaglandine E₂ en serotonine leidde tot verhoging van het aantal MMC's en de snelheid van voortgeleiding van fase III van het MMC van het antrum tot aan terminale ileum. De verandering in de frequentie van de actie potentialen in de sphincter van Oddi gedurende het toedienen van 16,16 dimetyl prostaglandine en serotonine correlerden ook met het MMC in het duodenum. Deze veranderingen in motiliteit van de tractus digestivus zouden verantwoordelijk kunnen zijn voor de diarree die vaak gezien wordt na het toedienen van 16,16 dimetyl prostaglandine E₂ of bij verhoogde synthese van serotonine bij carcinoid tumoren.

Deze experimentele studies leidden tot de conclusie dat, ondanks het verschil in de motiliteit, de sphincter van Oddi en het duodenum, cyclische veranderingen in de frequentie van actie potentialen ondergaan die correleren met de verschillende fasen van het MMC. De correlatie van actie potentialen in de sphincter van Oddi en het duodenum werd gevonden gedurende de periode van vasten en na voeding, als ook tijdens het toedienen van de verschillende stoffen die werden onderzocht in deze serie experimenten. Veranderingen in de motiliteit van de sphincter van Oddi na het toedienen van verschillende soorten voedsel of gastro-intestinale hormonen kunnen mogelijk een rol spelen in de regulatie

van de afvloed van gal en pancreas sappen naar het duodenum. De stoornissen in de elektrische activiteit van de sfincter van Oddi na toediening van alcohol zou kunnen bijdragen tot dysfunctie van de sfincter van Oddi.

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8. Coelho JCU, Gouma DJ, Moody FG, Li YF, Weisbrodt NW.
Serotonin increases the velocity of propagation and
frequency of the migrating myoelectric complexes.
Submitted for publication.

CURRICULUM VITAE

Julio C.U. Coelho was born on March 22, 1953 in Brazil.

He finished his medical school at the Federal University of Parana, Brazil in 1976. At graduation, he received the Prize Hildebrando de Araujo.

He finished his surgical residency at the Clinical Hospital of the Federal University of Parana in 1979 under the direction of the Prof. Dr. Giocondo V. Artigas.

He was a Clinical Fellow at the Department of Surgery of the University of Illinois at Chicago for 3 years under the supervision of Prof. Dr. Bernard Sigel and Prof. Dr. Lloyd M. Nyhus. Received Honorable Mention of the Chicago Surgical Society in 1981 and 3rd Prize of the Sigma Xi Graduate Student Research Forum of the University of Illinois in 1982.

He joined the Department of Surgery of the Federal University of Parana in March, 1982 as Assistant Professor and in the same year was promoted to Associate Professor.

From August of 1983 up to present, he has been working at the Department of Surgery of the University of Texas as Visiting Assistant Professor under the supervision of the Prof. Dr. Frank G. Moody.