

Mechanisms controlling the gastrointestinal migrating motor complex

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Abstract: The mechanisms controlling the migrating motor complex (MMC) are composed, and so far incompletely recognized. The central portion of the autonomic nervous system exerts rather modulatory effects upon the MMC although the strong inhibitory effects were also observed. The role of the enteric nervous system in the initiation and propagation of the MMC is crucial. However, these peripheral mechanisms are coordinated with central influences exerted by the extrinsic nerves. The basic role of the cholinergic system is thus combined with the adrenergic and non-adrenergic non-cholinergic influences. The hormones appear mainly to disrupt and convert the MMC cycle into the feed pattern. Several hormonal factors are also known to affect the MMC especially to induce its phase III.

Key words: migrating motor complex, central and peripheral neural control, hormonal control

Background. The migrating motor complex (MMC), also called the interdigestive migrating complex (IDMC), is a composed phenomenon and its phase III is the most characteristic of the whole cycle [1]. Its arrival and disappearance as well as duration of the cycle and of its individual phases are not stable and can be modulated by several factors [2]. Thus, the mechanisms controlling the MMC are composed and can be divided into the central and peripheral influences.

Central nervous control of the MMC. Currently, there is no doubt that the nervous control of the MMC is crucial for its initiation and modulation. It comprises the evident neural responses due to neuromediator's action and interplay among NANC-related central and peripheral modulators as well as the hormones (principally peptide hormones) [3, 4]. Central nervous control of the stomach and small intestine comprises mainly the effects mediated by extrinsic innervation of these regions, i.e. vagal and sympathetic nerve-related influences (Fig. 1). These actions mediated by the efferent nerves occur as the response to central effects and peripheral (afferent) stimuli from the gastrointestinal tract. One of the incompletely resolved questions is: what is the precise role of the central effects *vs.* the peripheral nervous influences in the control of the MMC cycle? There is increasing knowledge focusing on the role of the central nervous system in the control of the MMC that comprises the scientific evidence derived from physiological, pharmacological, surgical and clinical experiments and observations.

Physiological experiments performed in humans revealed that sleep does not abolish the MMC, although it is obvious that the nocturnal interdigestive cycle is reversibly modified, especially in normal conditions [5, 6]. Its phase I is prolonged at the expense of phase II, the amplitude of contractions and the spike bursts is lowered and the migration velocity of phase III of the MMC is slower. It occurs independently from REM

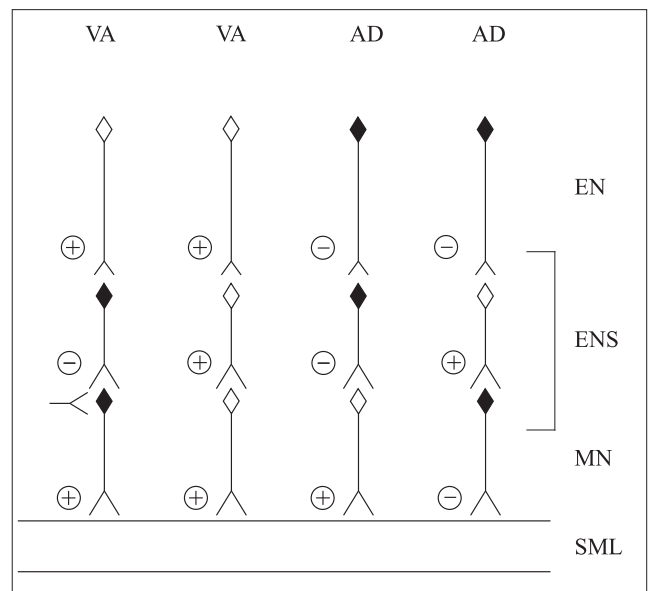


Figure 1 Scheme of the principal neural pathways controlling gastrointestinal motility.

VA vagus nerve
AD adrenergic nerve
EN extrinsic (preganglionic) neuron
ENS enteric nervous system containing interneurons
MN motor postganglionic neuron
SML smooth muscle layer of the gastrointestinal wall
+ stimulatory influences,
- inhibitory influences.

and non-REM sleep cycles. Another type of physiological experiments (sham feeding) showed that the MMC cycles were also not abolished, but in the post-sham-fed period the reappearance of phase III was retarded [7]. In other studies in man the effects of sham feeding were inconsistent. Soffer and Adrian [8] applied the sham feeding procedure and found an insignificant tendency for an increase in the MMC cycle duration. Poudroux et al. [9] found disruption of phase III of the duodenal MMC caused by sham feeding. Anticipation of feeding lowered the site of phase III origin to the jejunum and prolonged the duration of the MMC cycle [10].

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Pharmacological experiments comprise the effects of central administration of the various pharmacological substances upon the MMC. Results of earlier studies showed that intracerebroventricular (icv) administration of neurotensin in fasted dog converts jejunal MMC to the regular pattern occurring at a rhythm 2-3/h [11]. As an example, in rats, intracerebroventricular administration of such peptide as cholecystokinin octapeptide (CCK-OP) disrupted the MMC pattern; intrathecal administration of dermorphin induced the fasting pattern in the duodenum while somatostatin evoked only the modulatory effect [12, 13].

Another report from this centre revealed that intracerebroventricular administration of kentsin – a tetrapeptide extracted from 2-4 cell hamster embryos – restored the MMC cycle, and this response was antagonized by previous administration of naloxone [14]. More recent data indicate that the destruction of noradrenergic neurons by 6-hydroxydopamine administered intracisternally, intracerebroventricularly, and close to the locus ceruleus, exerted limited modulatory effects upon the MMC cycle [15, 16].

Surgical experiments, including sympathectomy, superior and inferior mesenteric ganglionectomy, as well as total extrinsic denervation of the gut, did not abolish the MMC, and these findings were summarized by the authors by stating that it is unlikely that the MMC is under the control of the central nervous system [17]. Similar results were obtained by Johnson et al. [18] who utilized the canine model with the autonomically denervated jejunum. The MMC cycles were preserved with increased frequency. Siadati et al. [19] completely denervated extrinsically the entire canine upper intestine, and the gastric component of the MMC was absent in one of the seven dogs. Recently published results of the experiments also performed in dogs with electrically damaged area postrema, showed that the antroduodenal MMC cycles were suppressed, i.e. cyclic, phasic and migratory patterns of the MMC were disrupted [20]. The effects of vagotomy upon the MMC are somehow different. Vagal cooling at the cervical level inhibited gastric cyclic motor activity and at the diaphragm level did not [21, 22]. Thus, Sarna [1] concluded that the extrinsic nerves, but probably not the vagus, might be important for the arrival of the gastric MMC. Chronic truncal vagotomy does not abolish the MMC but sometimes it inhibits MMC conversion to a fed pattern, decreases number of contractions and motility index of phase III of the MMC [23-25]. Acute interruption of vagal innervation may abolish gastric MMC [22]. This finding was confirmed in experiments during which the intraduodenal administration of capsaicin, one of the mediators of the afferent vagal fibers, inhibited gastric MMCs, either spontaneous or induced by motilin [26]. Although vagal efferent fibres are not numerous, the essential role of the vagal nerve in the control of the gastrointestinal MMC can be explained with the concept of 'command' neurons [27]. One vagal or adjacent non-vagal neuron can direct the function of several other intramural neurons. The alternative concept is that the divergent vagal input is able to exert a relatively broad modulatory influence over gastric neurotransmission [27].

The last group of experiments illustrating the central effects upon the MMC comprises some abnormalities within the central nervous system involving the interdigestive motility alterations. Stress seems to represent the most distinct example. As already stated above, the destruction of central noradrenergic neurons did not exert substantial effects on the

MMC. However, the limbic system represents the main locus of the control of intestinal function [28]. It also plays a central role in the control of emotions, including stress reactions. Prolonged stress inhibits the MMC cycle depending on the type, intensity, and duration of stress [29]. When the stressor power is substantial, inhibition of the MMC can be evident.

Therefore, in most cases, the central nervous system, appears to modulate the MMC cycle but it can also initiate and abolish the interdigestive motility pattern. Since complexes arriving in the stomach depend principally on input from cholinergic enteric neurons (including vagal efferent fibers), those originating in the small intestine depend rather on input from noncholinergic enteric neurons [30]. Thus, the central nervous system may control directly, although not exclusively, the gastric MMC, although its influence on small-intestinal MMC remains rather dubious.

Peripheral nervous control of the MMC. The question of the role of intrinsic gastrointestinal innervation in the control of the MMC seems to be devoid of basic controversy, and is believed to be greater than the extrinsic innervation. It has been recognized that some intramural presynaptic neurons have internal clocks generating the MMC when little or no nutritional load is present in the stomach and small intestinal lumen [31]. Complete neural isolation of the stomach can extinguish the MMC cycles. These cycles, originating in the stomach, may depend on input from cholinergic enteric neurons, apart from the other factors [1, 30]. These intramural neurons are most probably responsible for the initiation and migration of the MMC, as well as for the disruption of the MMC, at least in part [1, 31, 32]. After duodenectomy, the MMC was abolished in the stomach [33]. Apparently, the stomach does not have an independent MMC oscillator. Transection of the small bowel into multiple segments and completing the reanastomoses preserved the MMC cycling in all segments examined. In each segment, the MMC cycled independently with poor propagation [32]. Therefore, in these experiments, each segment of the gut was capable of MMC generating, which suggests that independent relaxation oscillators are present there. It seems likely that at least some neurons of the gut can oscillate spontaneously and generate a series of spike bursts to induce phase III of the MMC [31]. Furthermore, as mentioned above, fasting motor activity can be spontaneously generated after vagotomy and also by splanchnicotomy, especially in the small bowel [32]. These procedures can modulate the MMC cycle. While the vagotomy reduces duration of phase II and accelerates the MMC cycling, splanchnicotomy increases phase II periodicity. The MMC cycles also do not vanish following small bowel denervation and autotransplantation, they can only be modified [32, 34]. Denervation of the jejunoleum increases the MMC frequency while the autotransplantation exerts the opposite effect. Both these surgical procedures interrupt MMC coordination [35]. The MMC pattern can be abolished only after the rejection of transplanted allograft [35, 36]. Thus, it can be inferred from these studies that the neurons of the enteric nervous system play a crucial role in the control of gastrointestinal MMC.

Neurohormonal factors contributing to the control of the MMC. The nicotinic and muscarinic control of gastrointestinal motility is well known. The antimuscarinic drug atropine and the ganglionic blocker hexamethonium generally inhibit motor activity in the gastrointestinal region



in monogastrics and ruminants [37-39]. They affect the MMC cycle, and the character of the MMC primary response to these drugs is also inhibitory [37, 40-42]. Both these drugs immediately inhibited all spiking activity, the arrival of phase III of the MMC, and stopped the ongoing complexes. They also prevented the arrival of MMC cycles for 2.5-5 h. Similar effects were obtained when atropine or hexamethonium were administered locally [43]. However, after few minutes of complete spike burst inhibition, the stimulatory response – called rebound excitation – arrived mostly in sheep, but also occurred in other species [37, 39, 44, 45]. It has also been reported that atropine and hexamethonium are able to induce premature phase III of the MMC in the canine jejunum and ileum [46, 47]. There are probably species differences in the initiation of the rebound excitation. In contrast, pirenzepine at a relatively small dose induced the premature phase III of the MMC both in dog [48] and sheep [49]. Thus, pharmacological experiments confirm the importance of the cholinergic system in the control of the interdigestive motility.

The role of the adrenergic system in the regulation of the MMC is rather modulatory, although some of its meaningful influences upon the gastrointestinal motility, including the MMC cycle, have been described [1, 38, 50-52]. The sympathetic system is considered as the natural competitor of the parasympathetic system in the control of physiological functions, but with respect to the MMC, this does not seem to be the case [51, 53]. There are several adrenergic receptor subtypes [54] and their role in the control of the MMC has been incompletely recognized. Furthermore, the species and regional differences, possible cooperation with the cholinergic system and NANC regulators, as well as various responses to the given dose [38, 50, 55-58], make the problem complicated and difficult to explore. Since there are relatively few studies reported, the effect of the adrenergic system upon the MMC still remains largely unknown. Chung et al. [53] stated that the adrenergic blockade, performed in dogs with the use of phentolamine and propranolol, slightly increased the incidence of the MMC and decreased the number of contractions during phase III. Galligan et al. [51] did not confirm these effects, and found that in the guinea pig guanethidine increased the frequency of the MMC at the expense of shortening the duration of phase II. Local chemical sympathectomy with 6-OHDA also did not abolish the MMC but decreased its incidence at the expense of prolonging phase II. Altaparmakov and Wienbeck [50, 59] were among the first to study the role of α - and β -adrenergic receptors on the MMC and its phases. They administered the adrenergic regulators in man at the end of phase III of the MMC, and found that norepinephrine stimulated this phase mainly in the duodenum, including its propagation velocity. A similar effect was obtained after propranolol and phentolamine administration, suggesting that α -adrenergic receptors were responsible for these alterations [50]. Brikas [60] reported that the intravenous administration of the α_2 -antagonist, yohimbine, triggered phase III of the MMC in the ovine ileum, and this effect was antagonized by intravenous administration of naphazoline. Likewise, the α_1 -agonist phenylephrine also provoked the RSA phase in the ileum and this effect was blocked by prazosin. Another α_2 -agonist clonidine was able to induce phase III in man [38]. In canine jejunum it evoked the opposite effect to medetomidine, and these effects were reversed by atipamezole and yohimbine [61]. Isoprenaline in fasted humans [62] and isoproterenol in fed dogs [63], the unspecific β -agonists, inhibited or induced

phase III of the MMC, respectively, while propranolol did not evoke any significant changes in phase III of the MMC [62]. Studies on the rat small intestine revealed that isoprenaline inhibited the MMC cycle and induced irregular spiking activity, and this effect was blocked by propranolol or by the β_2 -antagonist ICI 118 551 [64]. However, acebutolol, a selective β_1 -antagonist, failed to antagonize the effect of isoprenaline. This negative effect was confirmed by administration of prenaterol (β_1 -agonist), while ritodrine (β_2 -agonist) mimicked the isoprenaline effect. Partial β_3 -agonist D7114, also given locally, disrupted the MMC pattern and did not induce any spiking activity. However, none of the antagonists used alone in this study, i.e. propranolol, acebutolol and ICI 118 551, induced changes in the MMC [64]. In sheep [65], the intravenous administration of isoprenaline and dobutamine (β_1 -agonist) induced phase III of the MMC in the jejunum, and the effect of dobutamine was antagonized by acebutolol. Ritodrine caused an inhibitory effect that was blocked by propranolol [65].

Among the other gastrointestinal mechanisms controlling the MMC, serotonin and serotonin receptors seem to play a pivotal role. Serotonin (5-hydroxytryptamine, 5-HT) is an important central neurotransmitter and the gastrointestinal mediator released in the gut from enterochromaffin cells [66]. Among the numerous 5-HT receptor subtypes, 5-HT_{1P}, 5-HT₃ and 5-HT₄ seem to be active in the control of the gastrointestinal motility [55,67]. 5-HT induces phase III in man, rat and sheep, but it is uncertain whether the same effect occurs in dog since 5-HT did not change the MMC cycles but increased motor activity only [68-71].

Intraduodenal 5-HT release fluctuates during the MMC cycle, but intraluminal 5-HT administration remains without any effect upon the contractile activity [68, 71]. The initiation of phase III of the MMC by 5-HT is mediated by 5-HT₃ receptors and, possibly also by 5-HT₄ receptors, especially in sheep in which the role of 5-HT₃ receptors in the control of MMC seems to be less important [69, 70, 72-75]. It is also possible that 5-HT₁ receptors are involved in the initiation of phase III of the MMC in man, as reported by Tack et al. [76]. However, this was not confirmed in the recent study [77]. Cisapride acts principally *via* 5-HT₄ receptors, thus its stimulatory action upon the gastrointestinal motility can be expected [78, 79]. However, there are also reports indicating that cisapride can trigger phase III of the MMC in physiological and pathological conditions [80, 81]. Metoclopramide is a drug acting *via* dopamine and cholinergic receptors, but it can also act through 5-HT receptors [82]. However, it can induce phase III of the MMC, independently of motilin release in man during physiological conditions, and in patients with diabetic gastroparesis [83], but this effect was not observed in dog [82, 84].

Nitric oxide is the omnipresent regulatory substance contributing to many functions in the body, including the central and peripheral nervous systems [85, 86]. It also functions as the recognized modulator in the enteric nervous system, and seems to play a role not only in the modulation of sphincter function but also in the control of the gastrointestinal interdigestive motility [87]. Administration of the inhibitor of the nitric oxide synthase, N-nitro-L-arginine methyl ester (L-NAME), stimulated the frequency of cyclic motor activity in rabbit stomach and small bowel *in vitro* [88]. *In vivo* studies revealed that the intravenous infusions of the nitric oxide synthase inhibitors (L-NAME and N- ω -

nitro-L-arginine) increased the intensity of small-intestinal contractions, induced phase III-like activity, and shortened the MMC cycles in dogs, rats, sheep and chickens [89-92]. These effects were reversed by administration of nitric oxide donors, thus being inferred from an indirect studies only. Sarna [93] proposed that the nitroergic influences of gastric motility and emptying might occur *via* three different pathways: direct modulatory effect, central action (also vagal efferents), and involving the peptides releasing nitric oxide.

The other intrinsic mechanisms controlling the MMC cycle involve the naturally occurring peptide modulators acting within the enteric nervous system. The first comprise mainly opioid receptor-dependent and nitric oxide-dependent influences. There are three classes of opioid receptors. μ receptors appear to play the greatest role in the control of gastrointestinal motility, since they are most abundant in the myenteric neurons, while κ and δ receptors occur mostly in other regions, and the action of μ agonists upon the smooth muscle involves different mechanisms from the action of κ agonists [56, 94, 95]. The regulatory role of opioid peptides upon the MMC is possible [96] since the actions of their exogenous derivatives, for instance, morphine, loperamide or dermorphin are the most evident, which was further confirmed by administration of naloxone [13, 97]. Naloxone (μ -receptor blocker) given separately during the interdigestive state in the dog delayed the occurrence of phase III of the MMC [98]. Morphine, loperamide, dermorphine or trimebutine can induce the MMC pattern and inhibit the fed pattern [13, 97, 99]. Intraperitoneal administration of enkephalinamide in rats, the synthetic enkephalin analogue, delayed the arrival of the MMC pattern [100]. Thus, it is rather well established that the general character of opioid action upon the intestinal motility is inhibitory. They can increase the amplitude on nonpropulsive small-intestinal contractions and suppress the propulsive contractions [38].

Motilin and other compounds involving motilin receptors seemed to play an important role in the initiation of phase III of the MMC in man and dog but not in pig [101]. The hormone fluctuates in accordance with the MMC phases. In sheep, motilin induced phase III from the jejunum but its role seems also to be limited [102]. Phase III was evoked by motilin in the gastroduodenal region. A similar effect was obtained in dogs after administration of motilin non-peptide agonist [103]. The discovery of motilin receptors on the smooth muscle supported the hypothesis that motilin induces phase III directly. Later studies in man showed that motilin can induce phase III only in the antrum [104]. However, motilin did not stimulate contractions *in vitro*, its effect was blocked by anticholinergic drugs, and other neural factors were able to induce phase III [47, 48, 105]. 1-4 months after small bowel resection, the MMC cycle reappeared in the stomach and small intestine but there were no plasma motilin peaks [106]. Thus, it became clear that the motilin-dependent mechanism of initiation of phase III is composed, and its direct role in the gastroduodenal coordination is negligible. Further studies provided novel data suggesting that the enteric nervous system cooperates with motilin in the induction of phase III in the gastroduodenal region. It was found that motilin receptors in the antrum are localized principally in nerves, and motilin is released or acts *via* M_1 cholinergic receptors localized on neurons [107-109]. During *in vitro* study its release was stimulated by carbachol and inhibited by atropine and hexamethonium [110]. In rabbits, intravenous administration of motilin did

not modify antral activity but increased duodeno-jejunal motor activity [111]. These effects were resistant to atropine and hexamethonium, indicating that motilin acted directly on the smooth muscle. Thus, the initiation of phase III of the MMC by motilin in man and dog involves the neurocrine mechanism and its direct action upon the smooth muscle is to stimulate propulsive contractions distinct from phase III. Therefore, it is possible that motilin also plays a certain role in the occurrence of the series of contractions in the fed state, and its transiently more effective release during the fed state can be the reason for the known similarities and differences between phase II of the MMC and the fed pattern.

Macrolide antibiotics have been recognized as acting through the motilin receptors, and in human studies such compounds as erythromycin or clarithromycin induced a premature phase III of the MMC [112, 113]. It has been proposed that the induction of an activity front by erythromycin occurs due to the activation of intrinsic cholinergic neurons, as in the case of motilin. However, it is also possible that 5-HT and opioid receptors participate in the neurally mediated action of motilin upon the interdigestive gastric contractions [74, 114]. The action of ghrelin, similar to that of motilin, upon the interdigestive gastrointestinal motility in man and dog has been described since some similarities between these two peptides have been found [115-117].

Pancreatic polypeptide (PP) is another natural regulatory substance possibly involved in the control of the MMC. Plasma PP level fluctuates in concert with the MMC cycle, reaching its maximal values during phase II or phase III [118-120]. However, the effect of PP on interdigestive motility has not been established since controversial results have been presented by different authors: either strong stimulation of the MMC frequency in dogs and pigs by PP or inhibition in dogs was reported [121]. Further studies showed that PP inhibits the MMC cycle and the interdigestive motility [122], and it appears that PP can be considered as the motilin antagonist, at least in some aspects. PP level is enhanced in plasma in the course of the postprandial state, and the administration of PP antiserum did not affect the MMC but increased the spiking activity in fasted but not in the fed dogs [123]. The action of PP is mediated by the cholinergic system [121]. Other members of the PP family, e.g. neuropeptide Y (NPY) and peptide YY (PYY), may also affect the MMC and these effects are largely inhibitory [122, 124-126].

Somatostatin is another hormone released into the blood circulation in accordance with the MMC cycle, at least in the dog and some other species [120, 121]. In man, the results are inconsistent. Tomita et al. [127] showed that plasma somatostatin concentration was significantly higher during phases III and II than during phase I of the MMC, at least in 8-hour fasted subjects, while Näslund et al. [128] observed an increase in intraduodenal but not in plasma concentration of somatostatin before phase III of the interdigestive cycle. Direct somatostatin contribution in the regulation of the MMC cycle seems to be different in the stomach and small intestine. In the stomach, somatostatin or its long-acting analogue, octreotide, inhibits motor and myoelectric activity, thus also suppressing the MMC cycle [129, 130]. In the small intestine, somatostatin shortens the MMC cycle at the expense of its phase II and its analogue, octreotide, induces the premature phase III-like activity. These findings were confirmed in other studies [38, 121]. Somatostatin administered locally can induce ectopic activity fronts also during the fed state [131].



The mechanism of somatostatin action can either be direct, mostly engaging sst_2 receptor, or indirect, comprising the inhibition of acetylcholine and motilin release, and possibly other mechanisms (nitroergic) and hormones involved in the control of the MMC [38, 121]. In rat and mouse, somatostatin increases cycle length, and this effect is mediated by sst_2 receptors and seems to be independent of NO [132, 133].

Several other neurohormonal factors affecting the MMC can be listed, including the neurally-mediated actions of histamine, CCK, neurotensin, insulin, VIP, substance P, neurokinin A, galanin, among others [1, 38, 134-137]. They can induce either stimulatory but mostly inhibitory changes, and it is often the case that the same substance can evoke the opposite effect, depending on the animal species, dose, and the other factors such as the release of other regulatory substances. It is also possible owing to the synaptic coexistence of some modulators with the principal mediator and due to the different neuronal pathways transmitting stimulus from the first neuron. Furthermore, interconnections between the intramural ganglia forming the enteric nervous system increase the possibility not only for different responses to the given stimulus, but also for coordination of the gastrointestinal motility that is clearly visible in the case of the MMC. Newly discovered peptides such as ghrelin [116], xenin [138], and orexin A [89], can induce phase III from the small bowel. However, their precise mechanisms of action upon the MMC remain to be elucidated.

Hormonal influences on the MMC pattern. This part will be limited to the hormonal control of MMC disruption after a meal. There is general agreement that both neural and hormonal factors contribute to the disruption of the MMC in response to feeding, although humoral factors can be more important for the stomach than for the small bowel [32, 39, 139]. Vagal integrity seems to be essential for the transmission of central inhibitory input to the gastrointestinal tract through non-cholinergic efferent fibres. It was demonstrated that such peptides as CCK, neurotensin and NPY administered centrally inhibited the MMC cycle in dogs and rats [11, 12, 126]. Furthermore, sham feeding increased plasma concentrations of gastrin and neurotensin, indicating their role in the neurohumoral control of the shift of the interdigestive to digestive pattern [8]. Local neural influences seem to play an even greater role. As already mentioned, the oscillating neurons, sensitive to the luminal content and triggering the MMC, have been recognized in the gastrointestinal wall, and are inhibited by the presence of the substantial bulk of digesta [31]. The inhibition of these neurons by local administration of atropine, hexamethonium and xylocaine triggers phase III of the MMC [47]. It has been proposed that such hormones and peptides as gastrin, CCK, secretin, insulin, glucagon, PP, neurotensin, PYY, NPY, substance P, neuromedin-N, and gastric inhibitory polypeptide (GIP), whose plasma level may be elevated in response to feeding, can participate in the disruption of the MMC during the postprandial period [32, 140, 141]. However, the physiological meaning of these changes is unclear since most of these peptides act simultaneously as paracrine mediators, neuromodulators, and a few of them also as neurotransmitters.

Luminal influences on the MMC. Paracrine actions of the hormones released into the gastrointestinal lumen and the actions of afferent mediators have been mentioned

above. However, some other factors controlling the MMC can be discussed here. The first is the gastric or intestinal distension caused by liquid or solid content, which is the natural MMC-inhibitory response to food ingested at the end of the interdigestive period [142, 143]. In turn, the aspiration of gas and acaloric fluid that did not inhibit the MMC, reduced the amplitude of contractions during phase II and its duration, as well as an increased duration of phase I [144]. In sheep, normal feeding and overfeeding induced relatively unmarked alterations in the MMC during the postcibal period [45, 145-147]. Total parenteral nutrition and acaloric meal also inhibits the MMC in man, although the reported changes in gut hormone release, considered important in the MMC inhibition and induction of the fed pattern, i.e. gastrin, secretin PP, glucagon and GIP, were negligible [148, 149]. In dog, the inhibition of the MMC is transient and not complete [150, 151]. The MMC cycle is prolonged and the frequency of phase III is decreased in the stomach and duodenum, but not in the jejunum. The second intraluminal factor important for the control of the MMC cycle is intraluminal pH. It was found that instillation of acid into the stomach inhibited the motilin-induced phase III of the MMC in vagally innervated, but not in the vagally denervated gastric pouch in man [152, 153]. These changes were observed even when the plasma motilin level was elevated [154]. Contractions during phase II of the MMC were also depressed in the antrum [152]. Abomasal infusion of volatile fatty acids in sheep inhibited abomasal motility, while the evoking mechanism might be different [155]. The intraduodenal pH fluctuates in the course of the MMC cycle. While during phase I it remains relatively stable and neutral, during phase II it becomes lower and rises again at the end of phase II and during phase III of the cycle [156]. When intraduodenal pH became acid, the inhibition of the gastroduodenal motility occurred, and the appearance of phase III of the MMC in the stomach was delayed [156, 157]. This is one of the reasons why the MMC cycles are irregular, and also probably why some of normal phases III of the MMC are ectopic. Intraduodenal administration of HCl solution induces the duodenal phase III of the MMC in man [158] and also in sheep [155, 159]. In these cases, vagotomy reduces (but does not abolish) acid-dependent inhibition of abomasal motility. However, it can prevent the arrival of the premature duodenal phase III, as observed in monogastric species. The intraduodenal alkali load also coincides with the duodenal phase III of the MMC [160].

Concluding remarks. The mechanisms controlling the MMC are still incompletely recognized and require extensive research to maintain progress in this sphere. Substantial development of available techniques facilitate recognition of the type of motor abnormality, which represents a good prognosis for the future and guarantees further progress in this area. The practical implications of the MMC rely on the possibility of recognizing normal and abnormal motor activity in pathological conditions [5, 28, 83], the study of motility-controlling central and peripheral mechanisms in normal and postoperative conditions [161, 162], and the study of the effects of new drugs and hormones on the interdigestive motility patterns [116, 138, 162-167].

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