Actions of Motilin on Gastrointestinal Motility and Plasma Immunoreactive Motilin Concentration in Interdigestive and Postprandial States

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Synopsis

Among biological actions of motilin on gastrointestinal motility, its action to induce phase III, activity front, of interdigestive myoelectric complex (IMC) appears to be of physiological significance. Synthetic motilin in a dose as little as 0.06 μg/kg-h was shown to induce phase III in dog. A cyclic increase in fasting plasma immunoreactive motilin concentration (PIMC) occurred in phase III in dog and in a later part of phase II in man, suggesting strongly that there is an intimate relationship between cyclic increase in fasting PIMC and IMC. The observation also suggested that gastric acid secretion increases in phase II and phase III of IMC. The cyclic increase in the acid secretion may be related to a coincidental cyclic increase in PIMC. Ingestion of a meat meal results in a significant decrease in PIMC and abolishes the cyclic increase in PIMC, while IMC changes to digestive pattern after a meal. The significant decrease in PIMC is not attributed to the 3 known gut hormones including gastrin, octapeptide of CCK and secretin.

When motilin, a 22 amino acid polypeptide, was originally discovered and isolated from the hog duodenal mucosa by Brown et al. in 1971, this hormone candidate was considered as an exciting agent that stimulates the contraction of gastric fundus in dog. As synthetic porcine motilin or its analogues had become available, its biological actions on the gastrointestinal tract were investigated by various groups of workers. Among the known biological actions of motilin or its analogue, its effect on the motility of gastrointestinal tract has been investigated extensively in recent years.

Action of motilin on gastrointestinal motility.

Motilin, given intravenously, stimulates contraction of the canine stomach (Brown et al., 1971; Jennewein et al., 1975; Lee et al., 1974), lower esophageal sphincter (Jennewein et al., 1975; Gutierrez et al., 1977, Meissner et al., 1976), and small intestine (Jennewein et al., 1975; Lee et al., 1974). Motilin was also shown to increase the number of spike potentials of myoelectric activity in the canine antrum and small intestine (Castrejana et al., 1978; Wingate et al., 1976). Among known gut hormones that stimulate motility such asmotilin, cholecystokinin and pentagastrin, motilin appeared to be the most potent one in terms of producing spike potentials in the canine antrum and duodenum (Fig 1) (Castrejana et al., 1978). In these studies, the dosage of motilin employed now turns out to be a pharmacological one. Another significant observation has been that motilin (Itoh et al., 1976; Lee et al., 1978) or 13-norleucine-
motilin (Wingate et al., 1976), induces phase III activity, activity front, in interdigestive state in dog. Indeed, a synthetic porcine motilin in a dose of 0.06 or 0.125 µg/kg-hr was able to induce phase III activity in dog (Fig 2). The dosage of motilin employed

Plasma immunoreactive motilin concentrations (PIMC) and % spike potentials on slow waves of the duodenum in a dog during intravenous infusion of saline and synthetic porcine motilin in a dose of 0.06 µg/kg-h. Hatched bars represent phase III of interdigestive myoelectric complex (IMC) during control period. A cyclic increase in PIMC (dotted line) coincided with phase III (hatched bar). Solid bars represent phase III during the experiment with i.v. infusion of motilin. Phase III (the right solid bar) was induced as PIMC increased to reach plateau level (solid line) (from Lee et al., Am. J. Dig. Dis. 23, 789, 1978).

(Lee et al., 1978) produced the plasma levels of immunoreactive motilin comparable to that observed in phase III of interdigestive myoelectric activity. Thus, this action of motilin on interdigestive myoelectric activity is probably a physiological one.

Plasma immunoreactive motilin concentrations, myoelectric activity and gastric secretion of acid in interdigestive state.

Using the immunoassay method (Bloom et al., 1976; Itoh et al., 1978; Tai and Chey, 1978), the plasma level of motilin has been measured and the relationship between the plasma levels of motilin and the proximal duodenal motility has been investigated. In the Fall of 1976, while we were investigating a possible relationship between plasma gastrin levels and phasic activities of interdigestive myoelectric complex, the motilin level revealed a cyclic increase and the peak concentration was observed in phase III of the proximal duodenal myoelectric activity in dog (Lee et al., 1978) (Fig 3). A similar observation was made by Itoh et al (Itoh et al., 1978). The cyclic increase occurred regardless of the
presence or absence of acid in the stomach (Fig 4) (Lee et al., 1978). Since our original reports (Chey et al., 1978; Lee et al., 1978), we have confirmed the identical observation in 15 additional dogs. Recently, it has been shown that a similar cyclic increase occurs in man also (Vantrappen et al., 1979; You and Chey, 1979). However, in the latter species, the motilin level peaked toward the end of phase II rather than phase III as occurred in dog. The mechanism of the cyclic increase in the motilin level in interdigestive state is not known at present time.

In addition to the changes in the motilin level in interdigestive state, we have observed a cyclic increase in gastric acid secretion which occurs in phase II and phase III of interdigestive myoelectric complex (Fig 5). The rise in acid secretion paralleled with the increase in the motilin level (Fig 3,4,5).

In view of our observations in dogs (Fig 6) (Chey et al., 1978) as well as in man (You and Chey, 1979) that atropine abolishes the cyclic increase of plasma motilin level, the release of endogenous motilin appears to be significantly influenced by the cholinergic nerve in interdigestive state. The mechanism of the cholinergic influence on the cyclic increase in the motilin concentration will require further investigation.

Effects of a meat meal and gut hormones on plasma motilin concentrations and myoelectric activity of the duodenum.

When the dogs were fed with a meat meal, the interdigestive myoelectric activity...
changes to digestive pattern that shows a uniform spike activity. Paralleled with the change in myoelectric activity, the plasma motilin concentration showed a steady and significant decrease, thereby, the cyclic increase was no longer present (Fig 7). The identical observation was made in 3 dogs (Lee et al., 1980). In order to determine a possible effect of three well known gut hormones on the cyclic increase in the plasma motilin level and interdigestive myoelectric activity, synthetic human gastrin I (G-17), GIH secretin and octapeptide of cholecystokinin (CCK-OP) were administered individually and a combination of the three. While both gastrin and CCK-OP converted interdigestive pattern of myoelectric activity to its digestive pattern, the cyclic increase in the plasma motilin concentration did not change. Secretin affected neither the cyclic increase of motilin nor interdigestive myoelectric activity. The combination of 3 hormones also failed to abolish the cyclic increase of motilin. Thus, none of these hormones that increase in the plasma after ingestion of a meal is responsible for the decrease in the plasma motilin levels during the postprandial period, namely the abolishment of cyclic increase in the interdigestive motilin level.

Comment

Although motilin or its biologically active analogues were shown to stimulate motility of the gastrointestinal tract, its action that induces phase III, activity front, of interdigestive myoelectric activity in dog appears to be of a physiological significance. Synthetic porcine motilin in a dose that occurs in phase III of interdigestive myoelectric complex was able to produce phase III in dog (Lee et al., 1978).

The cyclic increase in the fasting plasma motilin concentration occurs both in dog and man. The motilin concentration reaches the peak in phase III in dog and in the later part of phase II in man (Vantrappen et al., 1979; You and Chey, 1979). In both species, atropine given intravenously can abolish both cyclic increase in the motilin levels and interdigestive myoelectric activity. Based on these observations, motilin again does appear to play a significant role on the development of interdigestive myoelectric activity. The mechanism of action of motilin in this respect has not been clarified. An additional interesting observation has been that a cyclic increase in acid secretion occurs in dog also. Gastric acid secretion occurs as phase II begins and gradually increase to reach the peak in phase III. Whether or not this increase in the acid secretion is induced by a steady rise in motilin concentration remained to be investigated.

It is of interest to note that after ingestion of a meal, cyclic increase in the fasting motilin level was abolished and interdigestive myoelectric activity was converted to digestive pattern of myoelectric activity so that phase III, activity front, was abolished. The postprandial change in the plasma motilin levels, however, were not attributed to the three gut hormones that increase after a meal. Two of the three, gastrin and CCK-OP, could convert interdigestive myoelectric activity to digestive pattern. Thus, dissociation between cyclic increase in the fasting plasma motilin and phase III, activity front, of interdigestive myoelectric activity can occur. This dissociation cannot be explained adequately at
this time. The observation suggests, however, that the cyclic increase is not likely to occur as a result of phase III or phase III-like myoelectric activity.

Because of the cyclic increase in the fasting plasma motilin concentrations, it is expected to have significant variations in the plasma motilin levels depending on the time of blood sampling in the same dog or subject. Thus, one requires caution in interpreting the experimental data dealing with plasma motilin concentrations unless the experiment is designed to avoid this variation.

Little is known about the release of endogenous motilin at this time. In dog, motilin is not released in a significant amount by a meat-containing meal or hydrochloric acid in a physiological amount. Nor did we observe any effect of fat on the release of motilin, while a fat meal appears to increase plasma concentration of motilin in man (Mitznegg et al., 1976). Undoubtedly, research will continue to uncover factors that stimulate endogenous motilin release for years to come.

References


