Intraluminal Regulatory Peptides and Intestinal Cholecystokinin Secretion

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INTRODUCTION

Problems in Studies of Intestinal Cholecystokinin Secretion

The gastrointestinal hormone cholecystokinin (CCK) was purified from porcine intestinal mucosa and sequenced almost 30 yr ago (1), yet the lack of progress in understanding how CCK secretion is regulated is apparent when one compares what is known about the regulation of gastrin secretion with that established for CCK (2,3). This is more remarkable because gastrin, which is phylogenetically CCK’s younger sibling (4), was purified and sequenced from porcine antral mucosa a few years before CCK (5). Thus, whereas neural and paracrine pathways controlling gastrin secretion have been well-established (6), the mechanisms that mediate CCK secretion from the small intestine are relatively unclear.

Why is the study of putative neural, hormonal, or paracrine pathways regulating CCK secretion so difficult? In great measure, the multiple interactions among intraluminal pancreatic juice, gastric juice, and bile with ingested food have made elucidation of the pathways controlling CCK secretion particularly difficult. CCK secretion is inhibited by pancreatic endopeptidases (7–10), yet it is the digestive products of pancreatic endopeptidases acting on food that stimulate CCK secretion. Therefore, pancreatic enzymes need to be present to observe an optimal CCK secretory response to a meal (11–14). Furthermore, intact (undigested) proteins stimulate CCK secretion in the rat when pancreatic proteases are present (15–17), but protein hydrolysates (peptone), and not intact proteins, stimulate CCK secretion when intraluminal pancreatic proteases are absent (18–20). Fatty acids stimulate CCK secretion (15,21,22) and bile acids enhance fat digestion and solubilization of fatty acids, yet bile acids inhibit CCK secretion (23–30). Finally, gastric juice entering the proximal small intestine could directly or indirectly influence CCK secretion (31–33), and CCK secretion may also be affected by adaptive changes in pancreatic exocrine function (34,35).

Apparently, proteins and protein hydrolysates do not directly stimulate CCK release from intestinal CCK-secreting cells of the rat (36). This observation favors the involvement of an endogenous factor or factors in stimulation of CCK release in response to intraluminal nutrients. Monitor peptide, bombesin and GRP (18,36–40), have been examined as possible mediators in luminal nutrient-stimulated CCK secretion. Monitor peptide, bombesin, and GRP stimulate CCK secretion in vivo and in vitro and receptors for these peptides are found on intestinal CCK-secreting cells (38,41,42). However, it has not been shown that monitor peptide, bombesin, or GRP mediate CCK secretion in response to intraluminal nutrients (43,44). Another putative mediator of intestinal CCK release, luminal cholecystokinin releasing factor (LCRF), was recently described (45). The events leading to its discovery, purification, and chemical characterization are discussed in the next sections.

STIMULATION OF PANCREATIC GROWTH, PANCREATIC SECRETION, AND CCK RELEASE BY DIETARY PROTEASE INHIBITORS

Pancreatic Hypertrophy in Rats and Chicks Fed Raw Soybean Meal

The discovery of endogenous, luminal CCK releasing factors can be traced back to studies showing that heat-sensitive factors in soybean meal reduced food intake and induced pancreatic hypertrophy in chicks (46). This effect also occurred in rats, and the pancreatic hypertrophy persisted even when the growth inhibiting effect of raw soybean meal was overcome by supplementing the diet with essential amino acids (47). The heat-sensitive factor in raw soybean meal to which both growth inhibition and pancreatic hypertrophy were attributed was the soybean trypsin inhibitor (SBTI) of Kunitz, which is the more prevalent of the two major trypsin inhibitors in raw soybean flour (48). The effect of SBTI or raw soy flour on pancreatic growth was shown to occur in the mouse and hamster, but not in dog, pig, calf, monkey, or adult guinea pig (49,50). Searching for the mechanisms mediating the effects of dietary trypsin inhibitors on the pancreas eventually led to the discovery of endogenous, trypsin-sensitive CCK-releasing regulatory factors present in the intestinal lumen.