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Role of Gastric Receptors in Gastrointestinal Disorder

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Abstract

The established and potential roles of cholecystokinin1 and cholecystokinin2 receptors in gastrointestinal and metabolic diseases are analyzed, along with findings from human studies involving agonists and antagonists. While there is considerable evidence implicating cholecystokinin1R in various diseases such as pancreatic disorders, motility disorders, tumor growth, satiety regulation, and cholecystokinin-deficient states, its specific role in these conditions remains ambiguous. Conversely, the role of cholecystokinin2R in physiological (e.g., atrophic gastritis) and pathological (e.g., Zollinger–Ellison syndrome) hypergastrinemic states, its effects on gastric mucosa, and its involvement in acid-peptic disorders are well defined. Recent research also suggests a potential role for cholecystokinin2R in various gastrointestinal malignancies. Current data from human trials investigating cholecystokinin2R antagonists are presented, along with their potential therapeutic implications for these conditions. Additionally, the utilization of cholecystokinin2 receptors as targets for medical imaging is discussed. Despite being among the earliest discovered gastrointestinal hormones, significant advancements in our understanding of cholecystokinin and gastrin signaling have been achieved through structural characterization, pharmacological identification, receptor cloning (cholecystokinin1R, cholecystokinin2R), and the development of receptor antagonists. Further insights have been gained from studies involving receptor and agonist knockout animals, as well as the characterization of receptor location and gene expression. This review focuses on elucidating the roles of cholecystokinin and gastrin and their receptors (cholecystokinin1R and cholecystokinin2R) in gastrointestinal and metabolic diseases, with particular emphasis on human studies and the potential for utilizing these insights for the treatment of human ailments.

Keywords: Gastrointestinal, cholecystokinin (CCK), CCK1R, CCK2R, malignancies

INTRODUCTION

Various gastrointestinal (GI) tissues express cholecystokinin1R (CCK1R), cholecystokinin2R (CCK2R), or both receptors, with notable inter-species differences in their tissue distribution, indicating that findings from animal studies may not always be directly applicable to humans [1, 2]. In humans, CCK1R protein is present in the stomach mucosa, exocrine pancreas, and smooth muscle cells of the gallbladder, stomach, and intestine. Additionally, CCK1R mRNA has been detected in vagal afferent fibers, the adrenal gland, the kidney, and mononuclear blood cells. Conversely, human pancreatic acini exhibit minimal to undetectable levels of CCK1R mRNA and do not respond to CCK1R agonists. Human tissues also express CCK2R protein in the exocrine and endocrine pancreas, stomach mucosa, and muscularis, with CCK2R mRNA found in blood mononuclear cells, the adrenal gland, and vagal afferent fibers [3, 4]. CCK1R exhibits high affinity for CCK and sulfated CCK analogs but low affinity for gastrin, which is a less effective activator of CCK1Rs at physiological

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concentrations [5]. The receptor exists in high- and low-affinity states, each coupled to distinct intracellular signaling pathways. On the other hand, CCK2R demonstrates similar affinities for gastrin, CCK, and desulfated CCK analogs [6]. Given that postprandial serum gastrin levels surpass those of CCK, gastrin likely serves as the primary physiological ligand for most peripheral CCK2R receptors. Numerous specific agonists and antagonists have been developed for both receptors, some of which have been evaluated in humans under physiological conditions or in various diseases [7, 8]. These findings are illustrated in Figures 1 and 2.

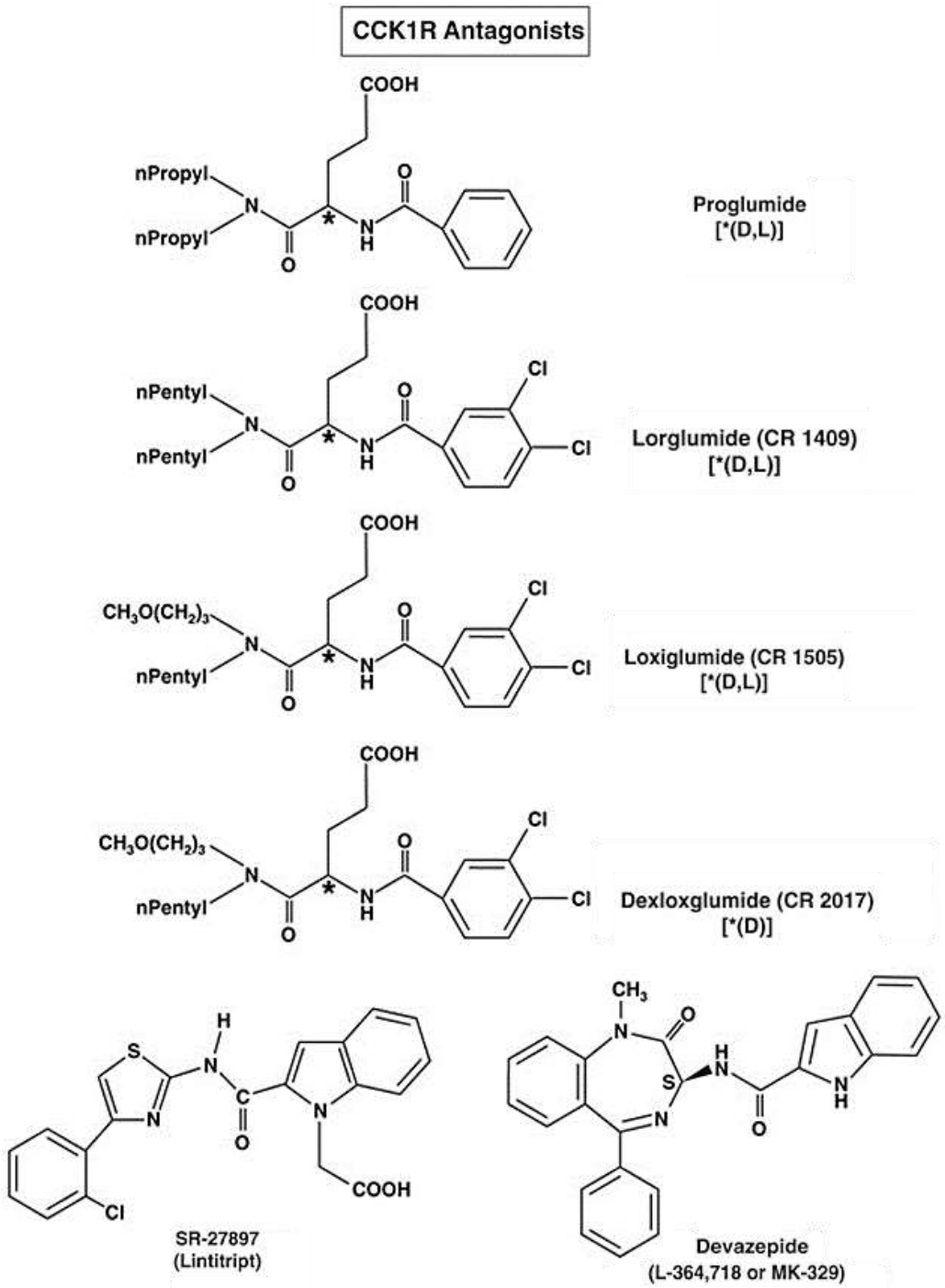

Figure 1. **Structure of CCK1 receptor antagonists used in human studies.** CCK1R and CCK2R affinities and chemical structures.

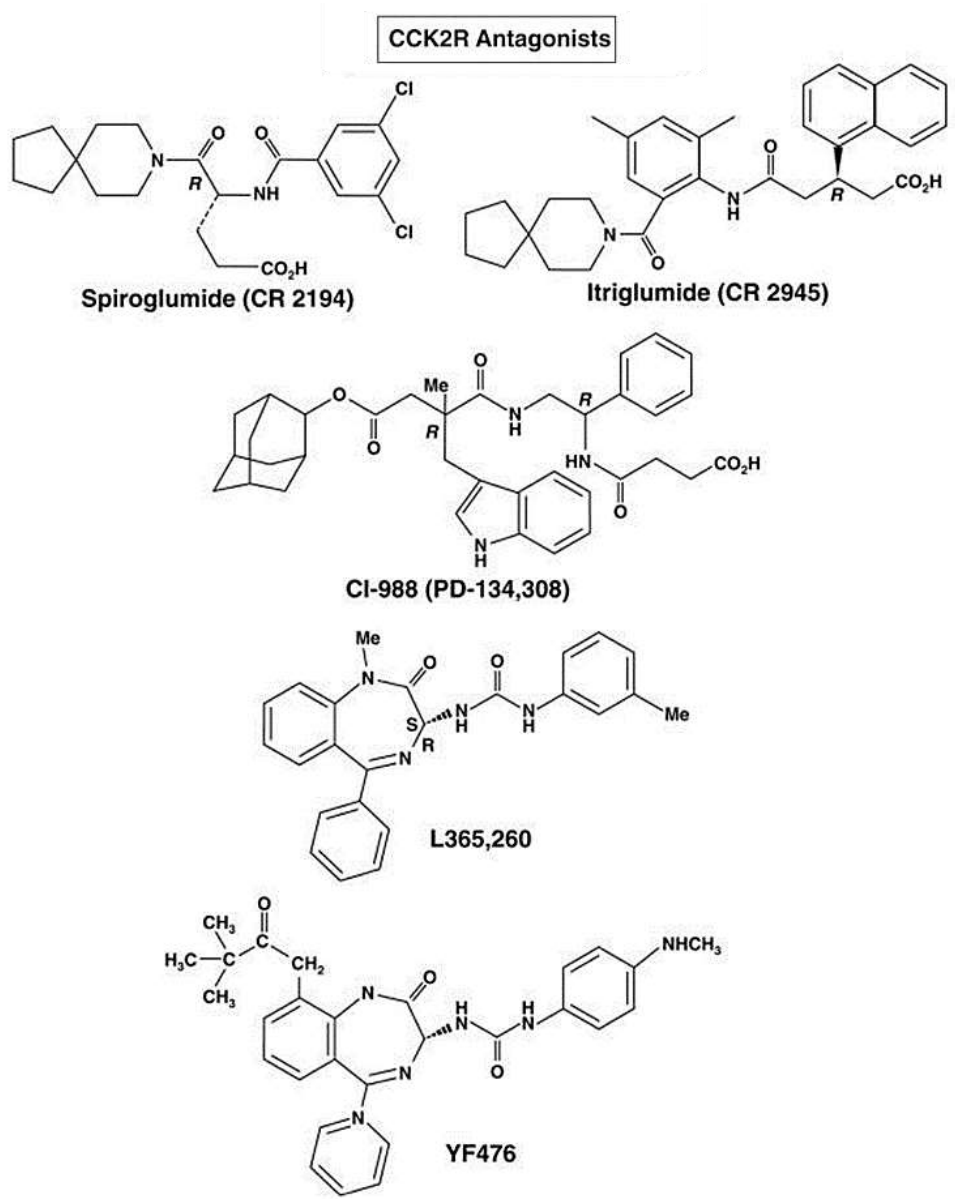

Figure 2. Structure of CCK2 receptor antagonists used in human studies.
CCK1R and CCK2R affinities and chemical structures.

GI Diseases Likely Involving CCK or CCK1Rs

Although CCK1Rs have been implicated in numerous GI conditions, their precise role in these disorders remains uncertain [9, 10]. While several studies suggest associations between CCK deficiency states and certain clinical manifestations, the involvement of CCK1Rs in pancreatic disorders (such as acute and chronic pancreatitis), GI motility disorders (including gallbladder disease, irritable bowel syndrome (IBS), functional dyspepsia, chronic constipation, and gastroesophageal reflux disease; GERD), as well as appetite/satiety regulation and pain modulation, has been proposed. However, the discussion regarding the latter two topics will be addressed in separate papers within this journal and will not be further explored in this review

CCK Deficiency States

Reduced serum levels of CCK, which may contribute to impaired gallbladder contractility and the development of cholelithiasis, have been documented in patients with conditions, such as celiac disease, short bowel syndrome, diabetes, infantile colic in newborns, and individuals receiving total parenteral

nutrition [11, 12]. In the latter group, there is debate regarding whether CCK administration can effectively prevent parenteral nutrition-induced cholestasis or the formation of sludge/stones. Some propose that diarrhea and malabsorption observed in patients with autoimmune polyglandular syndrome type 1 result from CCK deficiency caused by the loss of CCK-producing enteroendocrine cells in the proximal small intestine; however, this hypothesis has been challenged by others [13].

Role of CCK1R in Pancreatic Disorders

Role of CCK1R in Pancreatic Disorders General

The precise involvement of CCK1R signaling in clinical pancreatic disorders remains uncertain, primarily due to significant inter-species differences in pancreatic CCK1R and CCK2R expression. In rodent models, such as rats and mice commonly utilized in experimental studies of human pancreatic disease, pancreatic acini predominantly express CCK1R [14]. However, in humans, pancreatic acini express primarily CCK2R receptors, and CCK does not elicit any notable changes in human acinar cell function. Additionally, some studies suggest that CCK-induced pancreatic enzyme secretion in humans occurs through a cholinergic mechanism [15, 16]. Consequently, several researchers argue that CCK1Rs on human acini are unlikely to play a significant role in crucial cellular functions like enzyme secretion or proliferation, as observed in animal models [17, 18].

CCK1R in Acute Pancreatitis

CCK1R in Acute Pancreatitis General

Various lines of evidence from animal studies suggest that CCK1Rs may play a role in the initiation and progression of acute pancreatitis in experimental models [19]. Firstly, administration of supraphysiological doses of CCK agonists has been shown to induce acute pancreatitis in rats and mice. Secondly, in mouse models of acute pancreatitis induced by a choline-deficient ethionine-supplemented diet (CDE), CCK exacerbates the condition. Thirdly, OLETF rats lacking CCK1R expression exhibit less severe pancreatitis in multiple experimental models [20, 21]. Additionally, administration of CCK1R antagonists has been observed to reduce the severity of pancreatitis in most animal studies, although not consistently. Some studies even suggest that specific CCK1R antagonists could exacerbate bile-pancreatic-duct obstruction (PDO) pancreatitis in rats, possibly due to increased intra-acinar free-radical generation. Ethanol, a common cause of pancreatitis in humans, has been found to sensitize pancreatic acinar cells to CCK in rat studies [22, 23]. Furthermore, recent research indicates an up-regulation of CCK1Rs during pancreatic regeneration following taurocholate-induced pancreatitis in rats, suggesting a potential role for CCK1R in pancreas regeneration.

However, limited data exists regarding the pathogenesis of the most prevalent forms of pancreatitis in humans, such as those induced by biliary tract disorders, alcohol, drugs, and metabolic abnormalities. Indirect evidence suggests a potential role of CCK1Rs in clinical pancreatitis, such as higher serum CCK levels observed in patients with biliary pancreatitis compared to controls [24, 25]. Additionally, studies on hereditary pancreatitis indicate a correlation between mutations in genes regulating zymogen activation and different forms of the disease, resembling findings in animal models of pancreatitis, including CCK-induced pancreatitis. Despite these parallels, the significance of CCK1R signaling in clinical pancreatitis remains unclear.

CCK1R Antagonists in Acute Pancreatitis

Currently, only one human clinical study has been conducted on a CCK1R antagonist in acute pancreatitis. This double-blind study involved 189 patients from 104 Japanese centers who were administered three different doses of the selective CCK1R antagonist loxiglumide intravenously twice daily. The study observed similarities in pain disappearance, changes in clinical symptoms (such as nausea and vomiting), alterations in physical findings, and serum amylase levels across all three dosage groups. Notably, serum lipase levels normalized more rapidly in the high-dose group, suggesting the potential utility of loxiglumide in acute pancreatitis treatment, particularly as reported side effects were rare and typically mild [26, 27]. However, the study's lack of a placebo group renders its conclusions

inconclusive. Loxiglumide has progressed to a phase III trial for acute pancreatitis, but data from this trial are currently unavailable. To date, no study has definitively demonstrated the clinical benefit of CCK1R antagonists in acute pancreatitis in humans.

CCK1R in Chronic Pancreatitis

CCK1R in Chronic Pancreatitis General

Animal studies in rats, chicken and pigs suggest that exocrine pancreatic secretion is regulated by a negative feedback mechanism [28, 29]. A CCK-releasing peptide stimulates secretion of CCK, which triggers pancreatic enzyme secretion. Pancreatic enzymes inactivate the CCK-releasing peptide in the duodenum, thereby reducing their own secretion in a negative feedback loop. Several findings have led to the proposal that the inhibition of this feedback mechanism in chronic pancreatitis could cause elevated CCK levels inducing excessive stimulation of pancreatic secretion with elevated intraductal pressure, causing abdominal pain. Firstly, some patients with chronic pancreatitis are reported to have higher basal CCK levels than healthy controls. Secondly, some studies of pancreatic enzyme preparations in chronic pancreatitis showed pain relief, especially in mild to moderate disease and minimal/no changes in ERCP [30]. Some authors propose that this pain-relieving effect of the pancreatic enzymes is mediated by feedback inhibition of CCK, probably by denaturation of CCK-releasing peptide by the pancreatic enzymes. The role of CCK in the pathogenesis of pain in chronic pancreatitis is however controversial [31, 32], as three studies of pancreatic enzyme preparations in chronic pancreatitis showed no decrease in abdominal pain.

CCK1R Antagonists in Chronic Pancreatitis

Data from a double-blinded, randomized, placebo-controlled study involving 207 Japanese patients with chronic pancreatitis are available, where three doses (300, 600, 1200 mg/day) of oral loxiglumide were administered. The study evaluated physical signs, clinical symptoms, and serum pancreatic enzyme levels. In the 600 mg group, significant reductions were observed in back/abdominal pain, as well as in serum amylase and trypsin levels. Additionally, improvements in abdominal tenderness/resistance were noted in all three dosage groups. Adverse side effects were rare and mostly mild to moderate in severity. The authors concluded that a daily dosage of 600 mg of loxiglumide may hold potential in the treatment of chronic pancreatitis [33]. However, they emphasized the need for further well-designed placebo-controlled studies with appropriate endpoints to validate this conclusion. Although a phase III trial of loxiglumide in chronic pancreatitis has been initiated, data from this trial are currently unavailable

Use of CCK2R Antagonists in Peptic Ulcer Disease/Acid Secretion

A number of CCK2R antagonists have been studied in man for their effect on acid secretion or in peptic ulcer disease.

Glutaramic Acid Derivatives

Proglumide, initially marketed by Rotta Laboratories (Italy) for the treatment of peptic ulcers before the widespread use of histamine H2 antagonists and proton pump inhibitors (PPIs), showed increased healing rates in some studies. Further studies on glutaramic acid analogs of proglumide led to the discovery of CCK1R antagonists, including lorglumide, loxiglumide, and dexloxiglumide, which were discussed in the previous section on CCK1R disease states [34, 35]. Additionally, CCK2R-preferring antagonists such as spiroglumide and itriglumide were developed. In intravenous administration, spiroglumide dose-dependently inhibited gastrin, sham, and meal-stimulated acid secretion in normal volunteers. Although spiroglumide had excellent oral bioavailability, its further development was halted due to its relatively low anti-gastrin activity in vitro and its poor selectivity for CCK2R compared to CCK1R [36]. Further studies on spiroglumide led to the development of itraglumide (CR 2945), which exhibited a 9000-fold higher affinity for CCK2R than CCK1R [37]. Currently, itraglumide is reportedly undergoing Phase 1 trials as both an anti-ulcer and anxiolytic agent.

Benzodiazepine Derivatives

Structure-function studies of asperlicin, the initial potent nonpeptide CCK1R antagonist, led to the identification of the highly selective CCAR antagonist, [38] L-364,718, and the CCK2R antagonist, L-365,260. L-365,260, which demonstrated activity after oral administration and had an extended duration of action, inhibited stimulated acid secretion in various animal models [39]. In a double-blind study involving eight normal human volunteers L-365,260 effectively inhibited gastrin-stimulated acid secretion, although its duration of action was not prolonged. Subsequent human studies aimed at assessing the potential anxiolytic effects of L-365,260 yielded disappointing results, largely attributed to its limited oral bioavailability [40]. Following this, additional derivatives of 1,4-substituted benzodiazepines (L-368,730, L-369,466, L-736,380, L-740,093, YM022) and 1,5-substituted analogs (GV1500013X, GV191869X, Z-360) were developed, exhibiting enhanced potency and bioavailability. However, there are no reported human studies assessing their effects on acid secretion or secretory disorders. YF474, administered as a single dose, demonstrated dose-dependent inhibition of gastric acid secretion in human volunteers, with a longer-lasting antisecretory effect compared to ranitidine [41]. In later human trials, when YF476 was administered twice daily for 7 or 14 days, there was initially a significant reduction in acid secretion. However, this effect diminished with repeated doses, and after 7 and 14 days, gastric acidity levels were not significantly different from those of the placebo group. The mechanism behind the loss of efficacy of YF476 with continued treatment was unclear. Nevertheless, this marked the first report of tachyphylaxis associated with prolonged use of a CCK2R antagonist in humans.

Peptoids

Parke-Davis scientists utilized the C-terminal tetrapeptide sequence of CCK/gastrin (Trp-Met-Asp-Phe-NH2) to develop a range of CCK2R antagonists. Among these, CI-988 (PD-134,308) emerged as one of the most potent and selective compounds, effectively inhibiting pentagastrin-stimulated acid secretion in animal experiments [42, 43] While CI-988 has been extensively studied in humans to explore its potential in preventing panic attacks, there is currently no research available regarding its impact on acid secretion in human subjects.

Other CCK2R Antagonists in Human Acid Secretory Studies

Several potent CCK2R antagonists have been developed, yet their efficacy in human acid secretory disorders has not been evaluated. These include ureido-acetamide derivatives (RP 69758, RP 72540, RP 73870, DA-3934, D51-9927), quinazolinone derivatives (LY-202769), benzazepine derivatives (CP 310,713), and compounds based on dibenzobicyclo [2.2.2] octane and bicycloheteroaromatic scaffolds (such as compounds 83, 86, 89, 91, JB93182) [44, 45]

The current role of CCK2R antagonists in the treatment of human peptic disease or GERD remains uncertain [46]. Effective classes of drugs such as histamine H2 receptor antagonists (e.g., cimetidine, ranitidine, famotidine) and PPIs (e.g., omeprazole, lansoprazole, esomeprazole, rabeprazole, pantoprazole) are widely available and generally successful in inhibiting acid secretion and treating these conditions [47, 48]. Moreover, these drugs boast excellent safety profiles with prolonged use in many patients. Therefore, additional acid-suppressant agents like CCK2R antagonists may not be necessary for most patients.

Furthermore, if the observed tachyphylaxis with repeated use of potent CCK2R antagonists like YF476 is a common response in humans to repeated dosing, it could significantly limit the therapeutic potential of these compounds for acid secretory disorders. The primary role of CCK2R antagonists in these prevalent diseases might lie in potentially preventing the hypergastrinemia that typically accompanies prolonged treatment with potent acid-suppressant medications like PPIs in GERD patients. Currently, the short-term risk of this hypergastrinemia (less than five years) is minimal, although its long-term implications remain unclear. Defining this risk will be crucial in determining the potential necessity for preventive measures with concomitant treatment using CCK2R antagonists.

CCK2R Abnormalities in Diseases

Mutations in the CCK2R gene have been identified in various cancers, including pancreatic, colon, and stomach cancers [49]. Specifically, a misspliced version of the CCK2R gene, characterized by the retention of intron 4, has been observed in pancreatic and colon cancers. In pancreatic cancer, this misspliced receptor form was associated with reduced levels of the U2 small nuclear ribonucleoprotein particle auxiliary splicing donor (U2HF35) [50]. The aberrantly spliced receptor exhibited constitutive activation and demonstrated trophic activity in cells expressing it, suggesting its potential role in promoting tumor growth.

Furthermore, frameshift mutations in the CCK2R gene have been detected in GI tumors with high microsatellite instability (MSI) [51]. These mutations were found in 19% of cases with MSI, including 23% of gastric cancers, 13% of sporadic colorectal cancers, and 20% of individuals with hereditary colorectal cancer. Notably, all tumors with CCK2R frameshift mutations also displayed similar mutations in other genes. Based on these findings, it has been suggested that the human CCK2R gene may represent a novel candidate target gene implicated in the development of a subset of MSI tumors, contributing to their tumorigenesis [52].

In obese individuals with diabetes, a study identified a V125I mutation in the CCK2R gene in two out of eighteen families affected by type-2 diabetes mellitus. When this mutated receptor was expressed in COS-7 cells, it exhibited heightened affinity for CCK and increased potency in activating phospholipase C. However, further investigation through co-segregation studies revealed that the mutation was not linked to the occurrence of diabetes or an early onset of the disease. Presently, the exact role of this CCK2R mutation in the development of either obesity or diabetes mellitus within these families remains uncertain.

Gastrin, Gastrin-Related Peptides on Normal and Tumor Growth (Non-ECL Cell Growth)

Several studies have shown that peptides related to gastrin can exert significant growth effects on various tumors [53]. However, this topic will be discussed in detail in another paper within this volume, so it will not be further explored here.

CCK2R Imaging for Localization of Disease

Recent studies, particularly those utilizing radiolabeled somatostatin analogs, have highlighted the potential of exploiting the overexpression of G protein-coupled receptors by tumors or other pathological conditions for localization and clinical evaluation, as well as for targeted delivery of therapeutic agents [54, 55] Furthermore, a significant number of small cell lung cancers, ovarian cancers, and astrocytomas have been found to exhibit overexpression of CCK2R. Consequently, several research groups have embarked on developing specific radiolabeled analogs of gastrin to assess CCK2R expression through imaging, providing insights into its localization and overexpression in vivo across various disease processes [56]. For instance, [111In-DTPA]-[D-Asp26, Nle28, 31]-CCK (26–33) and [111In-DTPA] minigastrin analogs have been reported to facilitate imaging of CCK2R-bearing medullary thyroid cancers in patients, as well as visualization of the gastric mucosa, which harbors a high density of CCK2R cells. However, whether this strategy will prove clinically beneficial for localizing these tumors or enabling peptide receptor targeting of cytotoxic agents, akin to somatostatin analogs used in tumors exhibiting somatostatin overexpression, remains uncertain at present [57].

Role of CCK1R Functional Dyspepsia

Role of CCK1R Functional Dyspepsia General

It is characterized by discomfort or pain experienced in the upper abdomen and represents a prevalent issue among patients in clinical settings. Those with functional dyspepsia commonly exhibit hypersensitivity to stomach distension. Chua et al. demonstrated that the infusion of CCK could elicit specific symptoms in patients with functional dyspepsia [58]. The ingestion of fat, which triggers CCK release, is frequently linked to dyspeptic symptoms, with the onset of symptoms coinciding with elevated plasma CCK levels [59]. In individuals without health issues, the CCK1R antagonist

loxiglumide has been shown to expedite both liquid and solid gastric emptying, while a CCK1R agonist, GI181771X, has been observed to prolong the emptying of solid contents from the stomach [60].

Role of CCK1R Antagonists in Functional Dyspepsia

In a study involving 28 patients with functional dyspepsia, conducted in a randomized, double-blind, and placebo-controlled manner, researchers discovered that oral loxiglumide provided notably superior relief from dyspeptic symptoms compared to placebo [61]. Similarly, in another double-blind study involving 12 patients with functional dyspepsia, intravenous dexloxiglumide demonstrated significantly better alleviation of dyspeptic symptoms induced by gastric distension and duodenal lipid infusions compared to placebo. However, larger-scale studies are required to validate these promising results.

Role of CCK1R in Chronic Constipation

Role of Chronic Constipation and CCK1R General

Several investigations have shown that CCK influences the functioning of colonic muscle [62]. While some studies in humans and animals suggest that CCK prolongs colonic transit time, others have found that normal levels of CCK do not affect transit in healthy individuals. In studies involving healthy volunteers, CCK1R antagonists have been observed to hasten colonic transit; however, no such acceleration in colonic transit was noted after administering CCK1R antagonists to patients with IBS [63].

Role of CCK1R in GERD

GERD and CCK1R General

Several studies, both in animal models and humans, have indicated that CCK may contribute to GERD by indirectly increasing transient lower esophageal sphincter (LOS) relaxations. This effect can occur through gastric fundal distension and a direct interaction with esophageal CCK1Rs, leading to lower basal LOS pressure [64, 65]. CCK1R antagonists like loxiglumide and lintript have been shown to counteract the effect of CCK on the human LOS. Loxiglumide, specifically, has been observed to significantly reduce transient relaxation of the LOS triggered by CCK infusions or mechanical distension. Numerous human studies have demonstrated that loxiglumide, a CCK1R antagonist, can decrease transient relaxations of the LOS induced by various means such as air or mechanical distension, CCK infusion, or ingestion of a fatty meal [66].

Use of CCK1R Antagonists in GERD

- *In a study involving 10 healthy volunteers and 9 patients with GERD, Trudgill et al. observed that loxiglumide significantly inhibited postprandial LOS relaxation compared to placebo in both GERD patients and controls [67]. However, the effect on acid exposure was only modest. Another study by Hirsch et al. examined 12 patients with morbid obesity and found that loxiglumide reduced postprandial LOS relaxation but did not significantly decrease episodes of transient LOS relaxations. Further well-designed trials with an adequate number of patients are required to determine the role of CCK1R inhibitors in GERD.*

CCK1R Gene Mutations

Several recent studies indicate that decreased expression or non-functional CCK1R receptors may predispose certain patients to cholecystolithiasis. Miller et al. identified a 262 bp deletion resulting in a non-functional receptor in an obese patient with gallstones. Miyasaka et al. found reduced CCK1R expression in gallbladders with stones compared to those without, and noted a polymorphism in the CCK1R promoter among gallstone patients, although this did not affect promoter activity [68]. They also observed increased gallstone formation in CCK1R knockout mice. Other studies reported decreased CCK1R expression in gallbladders of patients with gallstones and non-contracting gallbladders, as well as in those with gallstones and diabetes mellitus. Some recent studies suggest a potential link between CCK1R polymorphisms and obesity. Funakoshi et al. [69] noted a polymorphism in the CCK1R promoter correlated with higher body fat percentage and increased serum insulin and

leptin levels, though the mechanism remains unclear and the polymorphisms did not affect promoter activity in STC-1 endocrine tumor cells. Additionally, they reported an association between this CCK1R promoter polymorphism and midlife weight gain in men when combined with a β3-adrenergic receptor polymorphism [70]. However, the mechanism underlying this association remains uncertain. Marchal-Victorion et al. identified a V365I mutation in the CCK1R of obese diabetic patients, which showed decreased expression and reduced efficacy for activating phospholipase C when transfected into COS-7 cells, though its contribution to diabetes mellitus or obesity in these patients remains unclear [71].

CONCLUSION

A GI disorder is any condition that affects how the digestive system works. In the USA alone, it's estimated that these disorders affect around 60–70 million people each year, resulting in approximately 250,000 deaths annually. Symptoms associated with GI disorders can vary widely depending on the specific condition and its underlying causes, but typically include issues like constipation, bloating, stomach pain, and excessive gas. Common digestive ailments include celiac disease, chronic constipation, persistent diarrhea, GERD, IBS, ulcerative colitis, Crohn's disease, gallstones, chronic pancreatitis, diverticulitis, liver disease, peptic ulcer disease, and lactose intolerance. These conditions can greatly affect a person's quality of life, leading to discomfort, pain, and, if untreated, potentially serious complications. Prompt identification and management of GI disorders by healthcare professionals can help alleviate symptoms, enhance overall well-being, and prevent potential complications. With effective management and treatment approaches, individuals with GI disorders can enjoy healthier and more satisfying lives.

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Conflict of Interest

The authors have no conflicts of interest to declare.

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