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Role of CCK/gastrin receptors in gastrointestinal/metabolic diseases and results of human studies using gastrin/CCK receptor agonists/antagonists in these diseases

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Abstract

In this paper, the estabished and possible roles of CCK1 and CCK2 receptors in gastrointestinal (GI) and metabolic diseases are reviewed and available results from human agonist/antagonist studies are discussed. While there is evidence for the involvement of CCK1R in numerous diseases including pancreatic disorders, motility disorders, tumor growth, regulation of satiety and a number of CCK-deficient states, the role of CCK1R in these conditions is not clearly defined. There are encouraging data from several clinical studies of CCK1R antagonists in some of these conditions, but their role as therapeutic agents remains unclear. The role of CCK2R in physiological (atrophic gastritis, pernicious anemia) and pathological (Zollinger-Ellison syndrome) hypergastrinemic states, its effects on the gastric mucosa (ECL cell hyperplasia, carcinoids, parietal cell mass) and its role in acid-peptic disorders are clearly defined. Furthermore, recent studies point to a possible role for CCK2R in a number of GI malignancies. Current data from human studies of CCK2R antagonists are presented and their potential role in the treatment of these conditions reviewed. Furthermore, the role of CCK2 receptors as targets for medical imaging is discussed.

Even though cholecystokinin (CCK) and gastrin were among the first gastrointestinal hormones discovered [1,2], both their physiological roles as well as their roles in clinically relevant gastrointestinal diseases remain unclear and even controversial in many cases [3–6]. The structural characterization of CCK and gastrin [7,8], pharmacological identification [9–13] and cloning [14, 15] of CCK and gastrin receptors (CCK1R, CCK2R), characterization of receptor location, peptide and receptor genes, development of receptor antagonists and receptor/agonist knockout animals [16–21] have led to important advancements in our understanding of the physiological and pathophysiological role of CCK and gastrin signaling [3]. Most of these topics are dealt with in other papers in this volume. The present review will focus on the role of CCK and gastrin and their receptors (CCK1R and CCK2R) in gastrointestinal and metabolic diseases with special emphasis on human studies and the assessments and potential for their use for treatments for human diseases

1.INTRODUCTION

Multiple gastrointestinal tissues express CCK1R, CCK2R or both. Importantly, there is a relevant inter-species variation of the tissue distribution of CCK1R and CCK2R [4,22], so that data from animal studies cannot always be extrapolated to humans. The human CCK1R is expressed at the protein level in the mucosa of the stomach [23,24], the exocrine pancreas [25] and in smooth muscle cells of the gallbladder [26], stomach [24] and intestine [27,28].

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Moreover, human CCK1R mRNA has been reported in vagal afferent fibers [29], the adrenal gland [30], the kidney [22] and mononuclear blood cells [23]. In contrast to most animals, very low or non-detectable levels of CCK1R mRNA are expressed in human pancreatic acini and these cells do not respond to CCK1R agonists [4,31]. CCK2R protein has been demonstrated in the human exocrine [32] and endocrine [33] pancreas, the stomach mucosa [24] and muscularis [24]. Moreover, CCK2R receptor mRNA expression has been shown in human blood mononuclear cells [23], adrenal gland [30] and vagal afferent fibers [29].

The CCK1R has a high affinity (K_d in the nanomolar range) for CCK and sulfated CCK analogues but a low affinity (K_d in the micromolar range) for gastrin, which is a poor activator of CCK1Rs at physiological concentrations [34–36]. The CCK1R has been shown to exist in a high- and low-affinity state, which are coupled to different intracellular signaling mechanisms [3,17,37–39].The CCK2R has almost equal affinity for gastrin and CCK as well as for desulfated CCK analogues [3,17,37,38]. As postprandial serum gastrin values are 5- to 10-fold higher than those of CCK, gastrin is probably the physiological ligand of most of the peripheral (i.e. non-CNS) CCK2R receptors [3]. For both receptors, numerous specific agonists and antagonists have been developed (for reviews, see [6,21,40]). The CCK1R and CCK2R antagonists that have been assessed in humans (physiologically or in diseases) are shown in Fig. (1) and Fig. (2), respectively.

Numerous selective CCK1R agonists and antagonists have been developed [3,6,21,41–43]. CCK1R selective agonists include peptides (sulfated CCK analogues as will as CCK tetra-peptide analogues [A-71378, A-71623, AR-R 15849]), benzodiazepine derivatives (GSK compound GI 18177, GW 7178, GW 5823) and thiazole derivatives (SR 146131, SR 146131) [21,41,44–46]. CCK1R agonist have primarily been investigated in appetite control and will not be discussed here because this is covered in other papers in this volume. CCK1R selective antagonists include glutaramic acid derivatives (lorglumide, loxiglumide, dexloxiglumide, A-65186), 1,4-benzodiazepine derivatives (L-364,718 [MK-329, devazepide], pranazepide [FK-480], tarazepide), various conformationally constrained dipeptoid analogues, various 1,3-dioxoperhydropyrido[1,2-c]pyrimidine analogues, 1,3,5-substituted pyrrolidinones analogues (SC-50,998), 1,3,3-substituted indol-2-one derivatives (T-0632) as well as others identified by randon screening (SR-27,897[lintitript], TP-680) [6,21,45,47]. In the present review only CCK1R antagonists that have been used in humans will be discussed [Fig. (1), Table 3].

II. CCK AND CCK1R

II.A. Physiological functions mediated by CCK1Rs (Table 1)

In humans strong evidence suggests CCK1R activation is involved in the regulation of numerous physiological processes, including gallbladder contraction and sphincter of Oddi relaxation, stimulation of pancreatic secretion, inhibition of gastric emptying and acid secretion, lower esophageal sphincter relaxation, slowing of colonic motility and regulation of satiety [4,16,19,20,48–62].

II.B. Gastrointestinal (GI) diseases likely involving CCK or CCK1Rs (Table 1)

Although CCK1Rs have been reported to be relevant in various gastrointestinal diseases, the role of CCK1Rs in these conditions has not been firmly established [4,16,48]. Several studies reviewed below report CCK deficiency states that could have clinical relevance. Others suggest that CCK1Rs could be involved in various pancreatic disorders (acute, chronic pancreatitis); GI motility disorders including gallbladder disease, irritable bowel syndrome, functional dyspepsia, chronic constipation, gastroesophageal reflux disease; appetite/satiety regulation, modulation of pain and regulation of tumor growth. The latter two subjects will be treated in other papers in this journal and thus will not be dealt with further in the following review.

II.B.1. CCK deficiency states—Reduced serum levels of CCK, possibly contributing to impaired gallbladder contractility and cholelithiasis, have been reported in patients with celiac disease [63–68], the short bowel syndrome [69], in diabetics [70], in newborns with infantile colic [71] and in patients receiving total parenteral nutrition [30,72]. In this later group of patients, it is controversial whether CCK administration can prevent parenteral nutrition-induced cholestasis or sludge/stone formation [73–77]. It has been proposed that diarrhea and malabsorption in patients with autoimmune polyglandular syndrome type 1 are due to CCK deficiency induced by loss of CCK-producing enteroendocrine cells in the proximal small intestine [78], however, this proposal has been questioned by others [79].

II.B.2. Role of CCK1R in pancreatic disorders

II.B.2.a. General: The relevance of CCK1R signaling in clinical pancreatic disorders is not clearly defined. This has occurred because important inter-species variation of pancreatic CCK1R and CCK2R expression complicates the development of suitable animal models. While in rat and mice, the two animals used in most experimental models of human pancreatic disease, pancreatic acini express exclusively CCK1R, human pancreatic acini express almost 2exclusively CCK2R receptors [4,22,80–82] and CCK causes no alteration in human acinar cell function [31]. Other reports indicate that CCK-induced pancreatic enzyme secretion in humans is mediated by a cholinergic mechanism [83,84]. Therefore, several authors conclude that it is unlikely that CCK1Rs on human acini mediate important cellular functions, such as enzyme secretion or proliferation [31,83], as reported in animal models.

II.B.2.b. CCK1R in acute pancreatitis: ***II.B.2.b.1 CCK1R in acute pancreatitis.General:*** Several lines of evidence in animal studies suggest that CCK1Rs may mediate induction and development of acute pancreatitis in experimental models [55,85–87]. First, in rats and mice, parenteral administration of supraphysiological doses of CCK agonists can cause acute pancreatitis [88,89]. Second, in the CDE model of acute pancreatitis in mice (choline-deficient ethionine-supplemented diet), CCK worsens the pancreatitis [89]. Third, OLETF rats lacking CCK1R expression develop less severe pancreatitis in several experimental models [90,91]. Forth, administration of CCK1R antagonists reduced the severity of pancreatitis in most [87, 89,92–99] but not all [100–102] animal studies of experimental pancreatitis. One study [102] even showed that the specific CCK1R antagonist L-364,718 [Fig. (1),Table 3] worsened the course of bile-pancreatic-duct obstruction (PDO) pancreatitis in rats, but it has been criticized by others for methodological problems [103]. Another report by the same group suggested that CCK1R blockade by, L-364,718 could increase intra-acinar free-radical generation, thereby worsening PDO pancreatitis [104]. Fifth, ethanol, one of the common causes of pancreatitis in men, has been shown to sensitize pancreatic acinar cells to CCK in *in vitro* [92,105] and *in vivo* [106] rat studies. Moreover, recent studies reporting an up-regulation of CCK1Rs during pancreatic regeneration after taurocholate-induced pancreatitis in rats [107] and a delayed pancreatic regeneration in CCK1R deficient OLETF rats after ethionine-induced pancreatitis [91] suggest a possible role for CCK1R in pancreas regeneration. In animal studies, intracellular activation of zymogens appears to be one of the early events in the initiation of acute pancreatitis [93,108–111].

At present, little data is available on the pathogenesis of the most common forms of pancreatitis in man, i.e. pancreatitis induced by biliary tract disorders, alcohol, drugs and metabolic abnormalities. There is only indirect evidence for a potential role of CCK1Rs in clinical pancreatitis. First, patients with biliary pancreatitis have been reported to have higher serum CCK levels than control patients or patients with non-biliary acute pancreatitis [112]. Second, studies in hereditary pancreatitis support the role of premature zymogen activation in clinical pancreatitis, because different mutations of the cationic trypsinogen [113–115] and the serine protease inhibitor Kazal type 1 [116–118], two molecules regulating zymogen activation, have

been found to correlate with different forms of hereditary pancreatitis. This analogy to animal models of pancreatitis, including CCK-induced pancreatitis, might provide indirect evidence for the role of CCK in certain forms of clinical pancreatitis, but does not clearly establish the importance of CCK1R signaling in this disease.

II.B.2.b.2 CCK1R antagonists in acute pancreatitis: Currently, data are available on only one human clinical study of a CCK1R antagonist in acute pancreatitis [119]. In this double-blind study, 189 patients from 104 Japanese centers were treated with three different doses of the selective CCK1R antagonist loxiglumide [Fig. (1),Table 3], administered intravenously twice a day. Pain disappearance, changes in clinical symptoms (nausea, vomiting), changes in physical findings and changes in serum amylase were similar in all three groups. Serum lipase levels returned to normal more quickly in the high-dose group, suggesting that loxiglumide could be useful to treat acute pancreatitis, especially as the reported side effects were rare and usually mild. However, this study lacks a placebo group and therefore is inconclusive. Loxiglumide has entered a phase III trial for acute pancreatitis, however no data are currently available [42]. So far, no study shows unequivocally a clinical benefit of CCK1R antagonists in acute pancreatitis in humans.

II.B.2.c. CCK1R in chronic pancreatitis: ***II.B.2.c.1. CCK1R in chronic pancreatitis. General:*** Animal studies in rats, chicken and pigs suggest that exocrine pancreatic secretion is regulated by a negative feedback mechanism [112,120]. 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. First, some patients with chronic pancreatitis are reported to have higher basal CCK levels than healthy controls [121–123]. Second, some studies of pancreatic enzyme preparations in chronic pancreatitis showed pain relief [121,124], especially in mild to moderate disease and minimal/no changes in ERCP [125]. Some authors propose that this pain-relieving effect of the pancreatic enzymes is mediated by feedback inhibition of CCK [125], 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 [120,126], as three studies of pancreatic enzyme preparations in chronic pancreatitis showed no decrease in abdominal pain [120,127, 128].

II.B.2.c.2. CCK1R antagonists in chronic pancreatitis: Data on one double-blinded, randomized, placebo-controlled study of three doses (300, 600, 1200 mg/day) of oral loxiglumide in chronic pancreatitis in 207 Japanese patients are available [129]. Physical signs, clinical symptoms and serum pancreatic enzyme levels were evaluated. In the 600 mg group, back/abdominal pain, serum amylase and trypsin levels decreased significantly while in all three groups, the abdominal tenderness/resistance improved. Adverse side effects were rare and mostly mild to moderate. The authors concluded that 600 mg/day loxeglumide may be useful in the treatment of chronic pancreatitis. Further adequately designed placebo-controlled studies with appropriate end points are needed to confirm this conclusion. A phase III trial of loxeglumide in chronic pancreatitis has been started, but no data are available [42].

II.B.3. Role of CCK1R in motility disorders

II.B.3.a. Role of CCK1R in gallbladder disorders: ***II.B.3.a.1.General:*** Numerous studies evidence that gallbladders from cholesterol stone patients have a CCK contractile defect [130,131], due to altered membrane fluidity, which results in dysfunction of G-protein coupled transmembrane receptors, such as the CCK1R [130–132]. Moreover, recent studies in a

knockout mouse model [133] provide evidence that disruption of CCK1R signaling leads to enhanced gallstone formation. Furthermore, some clinical studies show reduced CCK1R expression in cholesterol stone patients with non-contractile gallbladders [134] and in diabetic patients with gallstones [135].

The role of CCK in acalculous gallbladder disease and the clinical entity itself as a cause of chronic abdominal pain are controversial [136–139]. Multiple approaches to study gallbladder emptying after CCK or a fatty meal, triggering release of endogenous CCK, to identify symptomatic patients with acalculous cholecystitis who might benefit from a cholecystectomy have led to contradictory results [136,137,140,141]. While some recent studies on CCK-cholescintigraphy, the most widely used of these tests in the United States, have found a good reproducibility [142] and a good prediction of the presence of acalculous chronic/acute cholecystitis [143], others have found that cholescintigraphy may only be of limited use [144]. Therefore, further investigations with standardized test procedures are needed to define the optimal methodology for studying gallbladder emptying.

II.B.3.a.2. CCK1R antagonists in gallbladder disease: Pain relief after oral administration of the CCK1R inhibitor loxiglumide has been first reported by Beglinger et al. in patients with biliary colic refractory to conventional therapy after extracorporeal shock-wave lithotripsy of gallbladder stones [145]. In a pilot study of 14 patients with biliary colic, Malesci et al. report significantly greater and faster pain reduction after 50 mg of intravenous loxiglumide than after standard intravenous anticholinergic treatment [146]. Further randomized double-blind trials with sufficient patient numbers are needed to confirm this finding.

II.B.3.b. Role of CCK1R in irritable bowel syndrome (IBS): ***II.B.3.b.1. Role of CCK1R in IBS: general:*** Numerous abnormalities of bowel motility, impaired sensitivity to gastric acid and visceral sensitivity have been described in IBS [4,147–150]. Some studies suggest that exaggerated release of CCK or altered responses to CCK could contribute to the symptoms of IBS [149,151–154]. A recent study provides evidence that the presence of intraduodenal lipids increases visceral sensitivity in constipation-and diarrhea-predominant IBS [155] and that CCK is a possible mediator of this effect.

II.B.3.b.2. Role of CCK1R in IBS: CCK1R antagonists in IBS: In a study involving eight healthy volunteers and eight patients with IBS, loxiglumide failed to inhibit the gastrocolic response in both patient groups [156]. In a pilot double-blind placebo-controlled multicenter study of 72 patients with IBS, 200 or 400 mg t.i.d. oral loxiglumide were administered for eight weeks. 400 mg were reported to cause a significant clinical improvement when compared to the placebo group or 200 mg group, especially in constipation-predominant IBS [157,158]. A recent study of the CCK1 selective antagonist dexloxiglumide [Fig. (1),Table 3] (200 mg t.i.d) in 36 women with constipation-predominant IBS found accelerated gastric emptying and slower ascending colon emptying, but no significant effect on overall colon transit or relief of IBS symptoms [159]. In a multicenter, randomized, placebo-controlled, double-blind phase II study of 405 patients of oral dexloxiglumide (200 mg t.i.d.), female constipation-predominant IBS patients responded significantly better to dexloxiglumide than to placebo and dexloxiglumide significantly improved clinical symptoms (pain, bloating, stool consistency) in constipation-dominant IBS patients. Furthermore, dexloxiglumide was generally well tolerated [160–162]. Two phase III studies involving 1400 women with constipation-predominant IBS found a trend towards a benefit of oral dexloxiglumide vs. placebo, but it did not reach statistical difference [163]. Results from another phase III trials of 1800 patients with constipation-predominant IBS are still pending [43]. To date, the usefulness of CCK1R inhibitors in the treatment of IBS remains unclear.

II.B.3.c. Role of CCK1R functional dyspepsia: ***II.B.3.c.1. Role of CCK1R functional dyspepsia.General:*** Dyspepsia is defined as a discomfort or pain in the upper abdomen and is a very common problem in patients in clinical practice [164]. Patients with functional dyspepsia often present with a hypersensitivity to distension of the stomach [165]. Chua et al. showed that infusion of CCK can reproduce specific symptoms in patients with functional dyspepsia [166]. Consumption of fat, which is known to release CCK, is often associated with dyspeptic symptoms and the indcution of symptoms is accompanied by a rise in plasma CCK levels (62,65). In healthy subjects, CCK1R antagonist loxiglumide has been found to accelerate liquid and solid gastric emptying [42], whereas a CCK1R agonist, GI181771X, has been found to delay gastric emptying of solids [167].

II.B.3.c.2. CCK1R antagonists in functional dyspepsia: In a randomized, double-blind, placebo-controlled study of 28 patients with functional dyspepsia, the authors found that oral loxiglumide relieved dyspeptic symptoms significantly better than placebo [166,168]. In another double-blind study of 12 patients with functional dyspepsia [165], intravenous dexloxiglumide relieved dyspeptic symptoms induced by gastric distension and duodenal lipid infusions significantly better than placebo. Larger studies are needed to confirm these encouraging findings.

II.B.3.d. Role of CCK1R in chronic constipation: ***II.B.3.d.1. Chronic constipation and CCK1R.General:*** A number of studies have demonstrated that CCK affects the activity of colonic muscle [169–171]. In human and animals a number of studies provide evidence that CCK increases colonic transit time [5,172,173], however, other studies found that physiological concentrations of CCK do not effect transit in healthy subjects [156,174]. In healthy volunteers CCK1R antagonists have accelerated colonic transit [48,175,176], however, no increase in colonic transit occurred after treatment with CCK1R antagonists in patients with irritable bowel syndrome [159,177].

II.B.3.d.2. Chronic constipation and CCK1R antagonists: A randomized, double-blind, placebo-controlled trial of 21 chronically constipated geriatric patients found a significant benefit (acceleration of transit time, increase in stool frequency, diminution of number of enemas) after three weeks of oral loxiglumide (800 mg 3 times daily) [178]. In another study in 8 younger men, dexloxiglumide 200 b.i.d. over 7 days partly reversed increased colonic transit time induced by fiber-supplemented liquid formula diet, suggesting it might be useful as pro-kinetic in patients with chronic obstipation [175]. However, larger studies are needed to confirm these findings.

II.B.3.d. Role of CCK1R in gastroesophageal reflux disease (GERD): ***II.B.3.d.1. GERD and CCK1R.General:*** Multiple studies have shown in animal models and man that CCK can contribute to GERD by increasing transient lower esophageal sphincter relaxations indirectly by causing gastric fundal distension as well as through a direct interaction with esophageal CCK1Rs result in lower basal lower esophageal sphincter pressure [179–186]. The CCK1R antagonists loxiglumide and lintript [Fig. (1),Table 3) can inhibit the effect of CCK on the human lower esophageal sphincter (LOS)[187] and loxiglumide can significantly decrease transient relaxation of the LOS caused by either CCK infusions or mechanical distension [5]. A number of studies in humans demonstrated that the CCK1R antagonist, loxiglumide could decrease transient relaxations of the LOS induced by various means (air or mechanical distension, CCK infusion, fat meal) [5,60,185,188].

II.B.3.d.1. Use of CCK1R antagonists in GERD: In a study of 10 healthy volunteers and 9 GERD patients, Trudgill et al. found that loxiglumide inhibits postprandial LOS relaxation significantly better than placebo in GERD patients and controls, however, there was only a modest effect on acid exposure [186]. In a study of 12 patients with morbid obesity, Hirsch et

al. found that loxeglumide reduced postprandial lower esophageal sphincter relaxation but did not reduce significantly episodes of transient lower esophageal sphincter relaxations [189]. Further well-designed trials with sufficient patient numbers are needed to define the role of CCK1R inhibitors in GERD.

II.B.4.CCK1R gene mutations—A number of recent studies provide evidence that reduced CCK1R expression or expression of a non-functional receptor could predispose a subset of patients to cholecystolithiasis. In an obese patient with gallstones, Miller et al. described a 262 bp deletion resulting in a non-functional receptor [85]. Miyasaka et al. [190] reported that CCK1R expression was decreased in gallbladders with stones when compared to gallbladders without gallstones and described a polymorphism in the CCK1R promoter in gallstone patients. However, this polymorphism did not influence promoter activity. The authors further show that CCK1R knockout mice had increased gallstone formation [190]. Another study reported that CCK1R knockout mice showed increased sludge and gallstone formation at 12 and 24 months of life when compared to wild-type mice [191]. Recently, decreased CCK1R expression in the gallbladder was reported in patients with gallstones and a non-contracting gallbladder [134] and in patients with gallstones and diabetes mellitus [135]. Some recent studies suggest that CCK1R polymorphisms might be related to obesity. Funakoshi et al. [192] report that a polymorphism in the CCK1R promoter [G to T (n-128) and A to G (n-81)] is correlated with higher percent body fat and increased serum levels for insulin and leptin [193]. However, the mechanism of this association remains unclear and polymorphic promoters did not affect CCK1R promoter activity when transiently expressed in STC-1 endocrine tumor cells [192]. In another study, the same group reported that this CCK1R promoter polymorphism is associated with midlife weight gain in men only when combined with a β_3-adrenergic receptor polymorphism [194], although the mechanism underlying this association remains unclear. Marchal-Victorion et al. reported a V365I mutation in the CCK1R of obese diabetic patients [195]. This mutated receptor demonstrated a decreased expression and a low efficacy for activating phospholipase C when transfected into COS-7 cells. However, it remains unclear whether this mutation contributes to diabetes mellitus or obesity in these patients.

III. GASTRIN AND CCK2R

III.A. General

Gastrins well-established physiological effects are mediating acid secretion and stimulation of gastric mucosal growth, especially the enterochromaffin-like cells (ECL) [4,18] (Table 4). Recent studies on CCK2R knockout mice demonstrate that inhibition of gastric emptying is likely also a physiological effect of gastrin[196](Table 4). In contrast to the CCK1R and CCK, the role of the CCK2R or gastrin has been defined in a number of gastrointestinal disorders (Table 4). Gastrin causes gastric mucosal growth/hyperplasia of gastric enterochromaffin-like cells (ECL cells), which can progress to the formation of carcinoid tumors [197–201]; stimulates gastric mucosal growth with increased parietal cells, and is a mediator of gastric acid secretion in acid-peptic disorders and in various gastric acid hypersecretory studies including Zollinger-Ellison syndrome (ZES) [202–208]. Studies suggest gastrin-related peptides also may have important growth effects on a number of GI malignancies, because they frequently overexpress or ectopically express CCK2R [209–213]. Furthermore, gastrin itself or gastrin-related peptides, interacting with either the CCK2R or an unknown receptor, may have growth effects in some tumors, especially colon cancer [209–217]. The effect of gastrin, CCK and CCK-R's in cancer is dealt with in a separate section in this volume, so it will not be dealt with further, except in the use of radiolabeled CCK/gastrin analogues for localization of various tissues/tumors over-expressing these receptors.

III.B. Gastrin or CCK2R alterations in clinical GI disease

CCK2R and /or gastrin is important in human hypergastrinemic states (Table 2,4), in acid-peptic disorders, in imaging disease processes over-expressing CCK2R's, and CCK2R mutations have recently been described which may mediate important abnormal growth effects. In a number of these conditions the possible utility of CCK2R antagonists has been proposed and in some cases studied in humans. Furthermore, there is a long established use of gastrin analogues in provocative testing to examine for medullary thyroid cancer (MTC) or to assess gastric maximal acid output (MAO) to aid in the diagnosis or management of various disorders of gastric acid secretion [218–221]. Each of these will be briefly dealt with in the following sections.

III.B.1. Gastrin analogues for provocative testing—A number of analogues of gastrin, primarily derivatives of the active C-terminal gastrin tetrapeptide sequence (Tyr-Met-Asp.Phe-NH_2) were used in humans, principally to assess maximal acid output (MAO) [221]. Currently, only pentagastrin (N-t-butyl oxycarbonyl-β-Ala.Tyr.Met.Asp.Phe-NH_2) is generally used for this purpose or as a provocative agent for medullary thyroid cancer [218–221]. Assessment of MAO was used much more frequently in the past than at present [220,221]. In the past the MAO was assessed for possible prediction of acid- peptic recurrences, for the diagnosis of Zollinger-Ellison syndrome and to determine the presence of pernicious anemia and other hypochlorhydria/achlorhydric states [220–223]. Today, although underutilized, it remains important in the differential diagnosis of hypergastrinemic states, especially in the differentiation between physiologically hypergastrinemia due to hypo-/achlorhydria and pathological hypergastrinemia due to disorders such as Zollinger-Ellison syndrome (Table 4) [220,222–224]. Medullary thyroid cancers (MTC) are derived form parafollicular C-cells of the thyroid and release calcitonin which is used to assess for the possible presence of MTC as well as the ability of pentagastrin to stimulate calcitonin release from these cells [218,219, 225]. MTC ectopically express CCK2R in 92% of cases whereas the other cells of the thyroid do not which is the basis of this widely used provocative test [226].

III.B.2. Gastrin and CCK2R in hypergastrinemic states

III.B.2.A. Gastrin and CCK2R in hypergastrinemic states-diseases: Human hypergastrinemic states result from two principal causes: a physiological response due to acid hypo-/achlorhydria occurring in such disorders as pernicious anemia/atrophic gastritis (Table 4), and in disorders causing hypergastrinemia with acid hypersecretion [203] (Table 4). Long-lasting hypergastrinemia in both categories can have clinical significance, because it can result in gastric ECL cell hyperplasia and the development of gastric carcinoid tumors [197,200, 227–230]. This consequence of hypergastrinemia is receiving increased attention, because a proportion of gastric carcinoid tumors can be malignant [59,231,232]. Hypergastrinemia with acid hypersecretion is significant because the acid hypersecretion can result in aggressive peptic ulcer disease. Hypergastrinemia with acid hypersecretion can be caused by a number of abnormalities (Table 4). The most frequent cause is *H. pylori* infections, because in a proportion of infected patients hypergastrinemia with hyperchlorhydria develops[233,234]. The most aggressive hypersecretory disease occurs in the Zollinger-Ellison syndrome (ZES), which is due to the presence of a neuroendocrine tumor ectopically secreting gastrin (i.e., a gastrinoma) [203,224,235].

Various forms of gastrin peptides as well as gastrin mRNA has been reported in bronchogenic carcinoma, acoustic neuromas, pheochromocytomas, ovarian carcinomas, colorectal carcinomas, and other pancreatic endocrine tumor syndromes than those causing the Zollinger-Ellison syndrome [18,236–238]. Except for ovarian carcinoma and a single case of small cell lung cancer, these tumors do not cause ZES, because they do not secrete biologically active

amidated gastrins, which are the only forms that interact with high affinity with the CCK2R and stimulate potently acid secretion[18,236,238–242].

Gastrinomas producing the ZES until recently were thought to be entirely intra-abdominal in location (primary location: duodenum >pancreas >lymph nodes >liver >other abdominal sites) [224,235,243,244]. However, recent studies show gastrinomas can arise in the heart [245, 246] and ZES can also occur from gastrin secretion by a non-small cell lung cancer [239]. Because, patients with ZES are cured surgically in <50% of cases, the majority have life-long hypergastrinemia [59,244,247–250]. Furthermore, because their acid hypersecretion can now be controlled in almost every patient medically (i.e. with proton pump inhibitors, histamine H_2 antagonists) [59,251,251–253],today ZES patients rarely die of refractory peptic disease as they did in the past [254,255], and have extended survival; hence they are an excellent natural model to study the long-term consequences of hypergastrinemia in man.

Recent studies of ZES patients has provided important insights into the effects of chronic hypergastrinemia in man, especially in regards to its gastric effects [4,59,249]. These studies show hypergastrinemia can cause marked gastric acid hypersecretion which can result in severe refractory peptic ulcer disease, malabsorption and gastro-esophageal reflux disease [223,249, 254,256,257]; can cause increased gastric mucosal thickness and increased parietal cell mass 4- to 6-fold with no increase in peptic cells [258–261]; and result in a mean 2-fold increase in mucosal argyrophil cells [262–267]. Of the seven types of gastric endocrine cells the increase in gastric argyrophil cells with hypergastrinemia in man is due to an increase only in the gastric ECL cells [267], which is similar to results in animal studies [268–271]. No other clinical effects of chronic hypergastrinemia have been clearly demonstrated from studies of patients with Zollinger-Ellison syndrome, especially in regard to increased tumor growth or frequency of tumors in other sites [4,59,272,273]. These points will be discussed in more detail in the following sections.

A number of animal studies show that chronic hypergastrinemia (antisecretory drug treatment, gastrin infusions, surgical procedures) can cause gastric ECL proliferation and in some cases (rat, mouse, mastomys), the development of gastric carcinoids [198,270,271,274–278], which can occasionally be malignant [279]. It is proposed the gastric carcinoids arise from the ECL cell through a progression of ECL cell proliferative changes from increasing hyperplasia (linear, micronodular, adenomatoid) to dysplasia and carcinoid formation [200,270,280,281]. It is thought a similar sequence of events occurs in humans because various human conditions with chronic hypergastrinemia [especially atrophic gastritis/pernicious anemia and ZES (Table 4)] as well as in patients with chronic acid suppressive treatment, ECL cell proliferative changes can occur [200,230,263,266,270,280,282–287]. In addition, in patients with atrophic gastritis [231,284,287,288] or with ZES with multiple endocrine neoplasia-type 1 (MEN1) [231] and rarely without MEN1 [231,249,289,290], gastric carcinoid tumors develop.

Recently, increasing attention is being given to the effect of chronic hypergastrinemia on gastric ECL cell proliferation primarily for two reasons [59]. First, increasing numbers of patients with idiopathic gastro-esophageal reflux disease/peptic ulcer disease (PUD) are treated long-term with potent acid suppressants such as PPIs and in 80–100% of these patients [283,291] hypergastrinemia develops. In 20–30% of patients the fasting gastrin levels can reach levels frequently seen in ZES [249,283,291–293]. Second, in a subset (4–30%) of patients with hypergastrinemic states who develop gastric carcinoids, the tumors are malignant [231,232, 294].

A recent study [230] in 106 ZES patients provided a number of insights into the long-term effects of hypergastrinemia on gastric ECL cells in man. Because these patients infrequently have gastritis or gastric atrophy, as occurs in atrophic gastritis and which can effect ECL cell

behavior, they are a good model to study the effects of chronic hypergastrinemia alone in man [230]. Furthermore, at least one-half of the ZES patients have fasting gastrin levels in the range seen with chronic PPI treatment [230,249,282,291,293]. In this study [230] only 1% of the patients with active disease had a normal ECL cell pattern and 52% having at least linear hyperplasia or a more advanced ECL change [230] including 7% with dysplasia and 0% with carcinoid tumors [230]. Fasting gastrin levels correlated closely with the magnitude of the ECL change ($p < 0.0001$) and no threshold effect of gastrin on ECL cell hyperplasia was found, as proposed by others [200,295,296]. In contrast to animal studies, gender [274,297,298], age, or vagal tone [198,299,300] did not affect the degree of ECL change. These results show the risk of developing gastric carcinoids with chronic hypergastrinemia alone in man is low; however, even mild chronic hypergastrinemia in man can cause ECL hyperplasic changes without a threshold effect.

III.B.2.B. Use of CCK2R antagonists in human hypergastrinemic states: Whereas it appears logical to consider treating human hypergastrinemic states with CCK2R antagonists and numerous papers have proposed such a use for them [6,40,301,302] there is very little data from human studies. Particularly appealing would be the ability to prevent the ECL hyperplasia that occurs in these states as well as the ECL changes seen after the long-term use of potent acid suppressant drugs such as the PPI's and therefore reduces the potential development of gastric carcinoids with long-term hypergastrinemia [59]. In animal studies a number of CCK2R antagonists have been shown to cause prompt inhibition of gastrin stimulated ECL-cell histamine and pancreastatin secretion and synthesis as well as gastrin-stimulated acid secretion [303]. A few studies have examined the effect of CCK2R antagonists on gastric acid secretion in humans, which will be discussed in the next section, but almost no data exist on their potential effective in hypergastrinemic states. Whether this potential clinical indication for a CCK2R antagonist would actually be clinically helpful in many of these patients is unclear at present. Whereas it is clear chronic treatment with PPI's increases ECL hyperplasia in many patients it is not established in what proportion, if any, its long-term use in man leads to the development of carcinoids [59,304–306]. Furthermore, except for ZES patients with MEN1 who develop gastric carcinoids in 13–43%, the proportion of patients with atrophic gastritis (2–8%) or with idiopathic ZES (<1%) who develop gastric carcinoids over many years is relatively low [4, 59,230,307]. Lastly, other forms of treatment currently exist for hypergastrinemic patients with carcinoids with the demonstration that parental somatostatin analogues can reverse the hypergastrinemia and even the carcinoids presence in these patients [308,309]. Proglumide (DL-4-benzamido-N,N-di-n-propylglutaramic acid) [Fig. (2), (Table 3], a low affinity CCK1R and CCK2R antagonist (K_d, 3=11 uM) [6,310,311] was given intravenously to 3 patients with ZES [312]. Proglumide was given as a bolus injection (50 mg/kg) and as a bolus followed by a continuous intravenous infusion (50 mg/kg/hr). It did not alter serum gastrin levels but inhibited acid secretion by 13–62%, which was less than the 83–86% inhibition caused by an infusion of the histamine H_2 receptor antagonist cimetidine (2 mg/kg/hr). It was concluded that proglumide is a weak inhibitor of acid secretion in these patients [312].

III.B.3. Gastrin and CCK2 receptors in peptic ulcer disease

III.B.3.A. Gastrin and CCK2 receptors in peptic ulcer disease/acid secretion: One of the most important physiological effects of gastrin is its ability to stimulate gastric acid secretion [18].Even though studies in various species show the parietal cell possesses CCK2R, most evidence suggests the principal pathway of stimulation of acid secretion by gastrin is by stimulating release of histamine from ECL cells [18,313,314]. That gastrin is the major hormonal mediator of the gastric phase of acid secretion [18] is supported by studies utilizing immuno-neutralization of circulating gastrin, which completely inhibits acid secretion stimulated by peptone or glucose-induced gastric distension [315]. Gastrin also plays a variable role in the cephalic and intestinal phases of acid secretion in different species [18]. CCK2R

antagonists in rats inhibit gastrin-stimulated acid secretion and histamine release from ECL cells [303,313,316]. In humans spiroglumide, a selective CCK2R antagonist [Fig. (2),Table 3], inhibited acid secretion stimulated by a meal as well as sham feeding stimulated secretion [317]. These results support an important physiological role for gastrin in regulating acid secretion in humans, as well as other species. The central role of the CCK2R in mediating the action of gastrin on acid secretion is also supported by the results of CCK2R and gastrin knockout studies in mice [19,53,318]. In both cases the mice have an elevated gastric pH and do not secrete acid in response to gastrin [53,318].

Gastrin also has a trophic effect on parietal cells and chronic hypergastrinemia results in an increased parietal cell mass [224,319,320]. This is important clinically because the parietal cell mass correlates with the maximal acid output [221]. In various chronic hypergastrinemic states in man, such as ZES, both increased parietal cell mass and an increased maximal acid output are frequently found and can contributed to the marked gastric acid hypersecretion that occurs [223,224,258–261].

Numerous studies demonstrate that *Helicobacter pylori* (*H. pylori*) infections are the principal cause of duodenal ulcer disease; however, the exact mechanisms by which *H. pylori* causes duodenal ulcer are still unclear [321–324]. Furthermore, the exact role of gastrin or abnormalities in gastric secretion in the development of *H. pylori*-mediated duodenal ulcer disease remain unclear [321–324]. A proportion of patients with duodenal ulcers have an increased parietal cell mass resulting in an increased MAO, an exaggerated acid and gastrin release with meals or gastrin-releasing peptide administration, an altered sensitivity to gastrin, impairment in inhibiting responses mediating secretion of acid and gastrin, in addition to an increased basal acid output in 30% of these patients [322].

Patients with duodenal ulcer disease caused by *H. pylori* characteristically have an antrum-dominant, body-sparing, non-atrophic gastritis [323,324], which results in increased acid secretion and gastrin release. The increased gastrin release is mediated primarily by an impairment of the acid-mediated inhibitory control of gastrin release, which is regulated by somatostatin release from antral D cells [323–325]. Lower levels of somatostatin-IR are found in the antral mucosa of *H. pylori* infected subjects and the levels increase post-eradication of the *H. pylori* [323–325]. Functional studies suggest that alterations in the ability of CCK functioning through CCK1R may be involved in the impairment of acid-mediated inhibitory control of gastrin release in *H. pylori* infected subjects [326,327]. CCK acting via CCK1R on antral D cells stimulates somatostatin release, which has an inhibitory effect on gastrin secretion from antral G cells [50,323,328]. The CCK1R antagonist, loxiglumide (Table 3), increased meal-stimulated acid output in healthy controls, but not in duodenal ulcer patients [327]. Eradicating *H. pylori* results in correction of the abnormal response to CCK1R blockage in duodenal ulcer patients [326,327]. The mechanism by which *H. pylori* infection or accompanying gastritis alters the acid-inhibitory control of gastrin release and somatostatin levels is not completely clear [323,324]. Possible mechanisms include secondary to increased cytokine production, and alterations induced by ammonia production by *H. pylori* [317,323, 329].

Some studies [324], but not others [321], propose that alterations in gastrin regulation can explain most of the acid secretory abnormalities seen in patients with *H. pylori* infection. This includes the proposal that 1) the increased acid output is, in large part, due to the altered gastrin release, and this results in increased duodenal acid load which progressively damages the duodenal mucosa leading to gastric metaplasia and eventually to duodenal ulcers; and 2) the increased gastrin release results in an increased BAO and the trophic effects of gastrin cause the increased MAO [324].

III.B.3.B. Use of CCK2R antagonists in peptic ulcer disease/acid secretion: A number of CCK2R antagonists have been studied in man for their affect on acid secretion or in peptic ulcer disease.

Glutaramic acid derivatives: Proglumide, a non selective CCK1R and CCK2R low affinity antagonist (Table 3) was marketed by Rotta Laboratories (Italy) for treatment for peptic ulcers prior to the widespread use of histamine H_2 antagonists and PPIs and some studies reported increased healing rates [330–332]. Subsequent structure function studies of glutaramic acid analogues of proglumide yielded the CCK1R antagonists; lorglumide, loxiglumide, dexloxiglumide [Table 3,Fig. (2)] which are discussed in the previous section on CCK1R disease states, as well as the CCK2R preferring antagonists: spiroglumide and itriglumide [(Table 3), Fig. (2)]. Spiroglumide given intravenously in 3 doses (1,2.5,7.5 mg/kg/hr dose dependently inhibited gastrin, sham and meal stimulated acid secretion in normal volunteers [317] and in another study the inhibition of gastrin stimulated secretion was competitive in nature [333]. This drug was not developed further even though it had excellent oral bioavailability, because of it relatively low anti-gastrin activity in vitro and its poor selectivity for CCK2R compared to CCK1R[334]. Further structure-function studies of spiroglumide yielded itraglumide (CR 2945) which had a 9000 fold higher affinity for CCK2R than CCK1R (Table 3)[334,335] This compound is reported to now be in Phase 1 trials as an anti-ulcer and anxiolytic agent [6].

Benzodiazepine derivatives: Structure function studies of asperlicin, the first potent nonpeptide CCK1R antagonist [336] identified the highly selective CC_AR antagonist, L-364,718 [337] and the CCK2R antagonist, L-365,260 [338](Table 3). L-365,260 was active after oral administration, had a extended duration of action and inhibited stimulated acid secretion in a number of animals [339]. In a double-blind study in eight normal human volunteers, L365,260 inhibited gastrin-stimulated acid secretion, however the duration was not prolonged [340]. L-365,260 subsequently underwent a number of human studies assessing its possible anxiolytic effects, however it generally gave disappointing results, which were attributed to its limited oral bioavailability [6,341]. Subsequently, additional 1,4 substituted benzodiazepine derivatives (L-368,730, L369,466, L-736,380, L-740,093, YM022) as well as 1,5 substituted analogues (GV1500013X, GV191869X, Z-360) were developed [6,40,334,342] with enhanced potency and bioavailability, however no human studies assessing their effect on acid secretion/secretory disorders are reported with these compounds. YF476 (Table 3) was identified by structure-function studies of YM022 and shown to have a 5000 higher affinity for CCK2R than CCK1R, to have good bioavailability and to inhibit acid secretion in animals [302,343]. A single dose of YF474 caused dose-dependent inhibition of gastric acid secretion in human volunteers and the antisecretory effect was longer lasting than seen with ranitidine [344]. In later trials in humans when YF476 was administered twice per day for 7 or 14 days there was initially a substantial reduction in acid secretion, however this decreased with repeated doses and after 7 and 14 days in the two trials the gastric acidity was not different from placebo [345,346]. The mechanism of this loss of efficacy of YF476 with continued treatment was not clear. However, this is the first report of tachyphylaxis with prolonged CCK2R antagonist use in humans.

Peptoids: Using the C-terminal tetrapeptide sequence of CCK/gastrin (Trp-Met-Asp-Phe-NH_2) Parke Davis researchers developed a series of CCK2R antagonists [6,347]. One of the most potent and selective was CI-988 (PD-134,308) (Table 3) which potently inhibited pentagastrin-stimulated acid secretion in animal studies [348,349].CI-988 has been examined in a number of human studies to investigate its ability to prevent panic attacks [350–353],however there are no studies on its effect on acid secretion in humans.

Other CCK2R antagonists in human acid secretory studies: A number of other potent CCK2R antagonists have been developed, but not assessed in human acid secretory disorders, including ureido-acetamide derivatives (RP 69758, RP 72540, RP 73870, DA-3934, D51-9927), quinazolinone derivatives LY-202769), benzazepine derivatives (CP 310,713) [6,40,334], dibenzobicyclo [2.2.2]octane and bicycloheteroaromatic scaffold-based analogues (compounds 83,86,89,91, JB93182) [6,354,355].

What the role for CCK2R antagonists in the treatment of human peptic disease or gastro-esophageal reflux disease at present is unclear [334,342,356]. There is a number of classes of drugs such as histamine H_2 receptor antagonists (cimetidine, ranitidine, famotidine) and proton pump inhibitors (omeprazole, lansoprazole, esomeprazole, rabeprazole, pantoprazole) that are generally very effective at inhibiting acid secretion and treating these diseases. PPI's have a long duration of action so that there is in general not a need for an inhibitor that might even have longer duration of activity. Furthermore, each of the above compounds has an excellent safety record with prolonged use in many patients. Therefore an additional class of acid-suppressant agents such as the CCK2R antagonists is not need in most patients. Furthermore, if the tachyphylaxis seen with repeated use of YF476 [345,346] is a characteristic acid secretory response in humans to repeated dosing with a potent CCK2R antagonist, this will greatly limit the therapeutic potential of these compounds for acid secretory disorders. The main role for CCK2R antagonists in these common diseases might be to possibly prevent the results of the hypergastrinemia that occurs in almost all patients with prolonged treatment with potent acid anti-suppressants such as PPI's in gastroesophageal reflux patients [59].At present the risk of this hypergastrinemia short term (<5 years) is very low, although the long term risk is unclear [59,357,358]. The definition of this risk will be important in assessing the possible need for prevention of this effect with concomitant treatment with CCK2R antagonists [59].

III.B.4. CCK2R abnormalities in diseases—CCK2R mutations occur in a number of cancers including those of the pancreas [359], colon [113,114], and stomach [114]. A misspliced form of the CCK2R in which intron 4 is retained is reported in pancreatic [359] and colon cancer [113]. The occurrence of the misspliced receptor form was associated with decreased amounts of the U2 small nuclear ribonucleoprotein particle auxiliary splicing donor in pancreatic cancer [359] (U2HF35) [359]. The abnormal spliced receptor showed constitutive activation and had trophic activity in cells expressing it [113], suggesting its presence might confer t growth-promoting effects. In 43 gastrointestinal tumors with a high microsatellite instability, frameshift mutations were found in the CCK2R in 19% [114]. Frameshift mutations in the CCK2R occurred in 23% of gastric cancers, 13% of sporadic colorectal cancers and 20% of hereditary colorectal carriers, and all tumors also had frameshift mutations in other genes [114]. The LoVo colorectal cancer cell line responds to gastrin also showed a similar frameshift mutation in the CCK2R [114]. The above results [114] led the authors to propose that the human CCK2R gene is a new candidate target gene possibly playing a role in the tumorigenesis of a fraction of MSI tumors.

In obese, diabetic patients, 2 of 18 families with type-2 diabetes mellitus were found to have a V125I mutation in the CCK2R [195]. This mutated receptor, when expressed in COS-7 cells, had an increased affinity for CCK and enhanced potency for activating phospholipase C [195]. Co-segregation studies showed the mutation was not associated with diabetes or early age at diagnosis of the disease. At present, the role of this CCK2R mutation in the pathogenesis of either the obesity or diabetes mellitus in the families remains unclear.

III.B.5. Gastrin, gastrin-related peptides on normal and tumor growth (non-ECL cell growth)—Numerous studies demonstrate that gastrin related peptides can have important growth effects on a number of tumors [4,201,209–211,215,217,319,360]. This is dealt with in another paper in this volume so it will not be dealt with further here.

I.C. CCK2R imaging for localization of disease

Recent studies especially with radiolabeled somatostatin analogues demonstrate that overexpression of G protein-coupled receptors by tumors or other disease processes can be used for localization, clinical assessment and for receptor directed delivery of therapeutic agents [361–364]. CCK2R receptors are overexpressed in a number of human tumors particularly medullary thyroid cancer, (92%), but also some gastroenteropancreatic tumors [226,365]. In addition, over-expression of CCK2R occurs in a significant number of small cell lung cancers, ovarian cancers and astrocytomas [365]. This has lead a number of groups to develop specific radiolabeled analogues of gastrin that could be used to assess CCK2R expression using imaging and provide information on its localization and over-expression in vivo in different disease processes [366–372]. [^{111}In-DTPA]-[D-Asp^{26}, Nle$^{28, 31}$]-CCK (26–33[366] and [^{111}In-DTPA] minigastrin analogues [368,372] are reported to image CCK2R bearing medullary thyroid cancers in patients as well as to image the gastric mucosa which contains a high density of CCK2R cells. Whether this approach will be clinically useful in localizing these tumors or in allowing peptide receptor targeting of cytotoxic agents, as has been done with somatostatin analogues in a number of tumors over-expressing somatostatin [361–364], is at present unclear.

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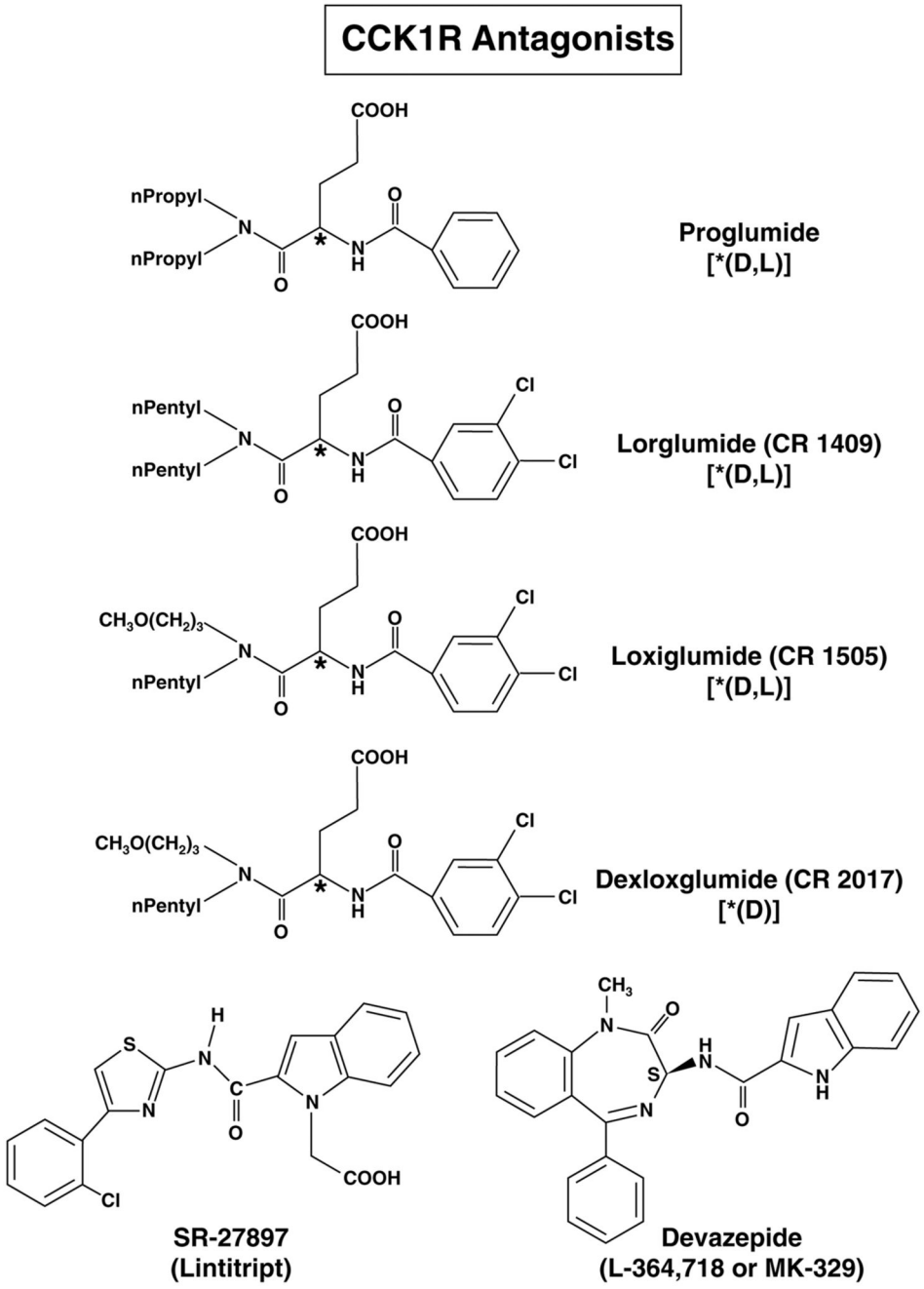

Figure 1.
Structure of CCK1 receptor antagonists used in human studies. CCK1R and CCK2R affinities, chemical structures and references are listed in Table 3.

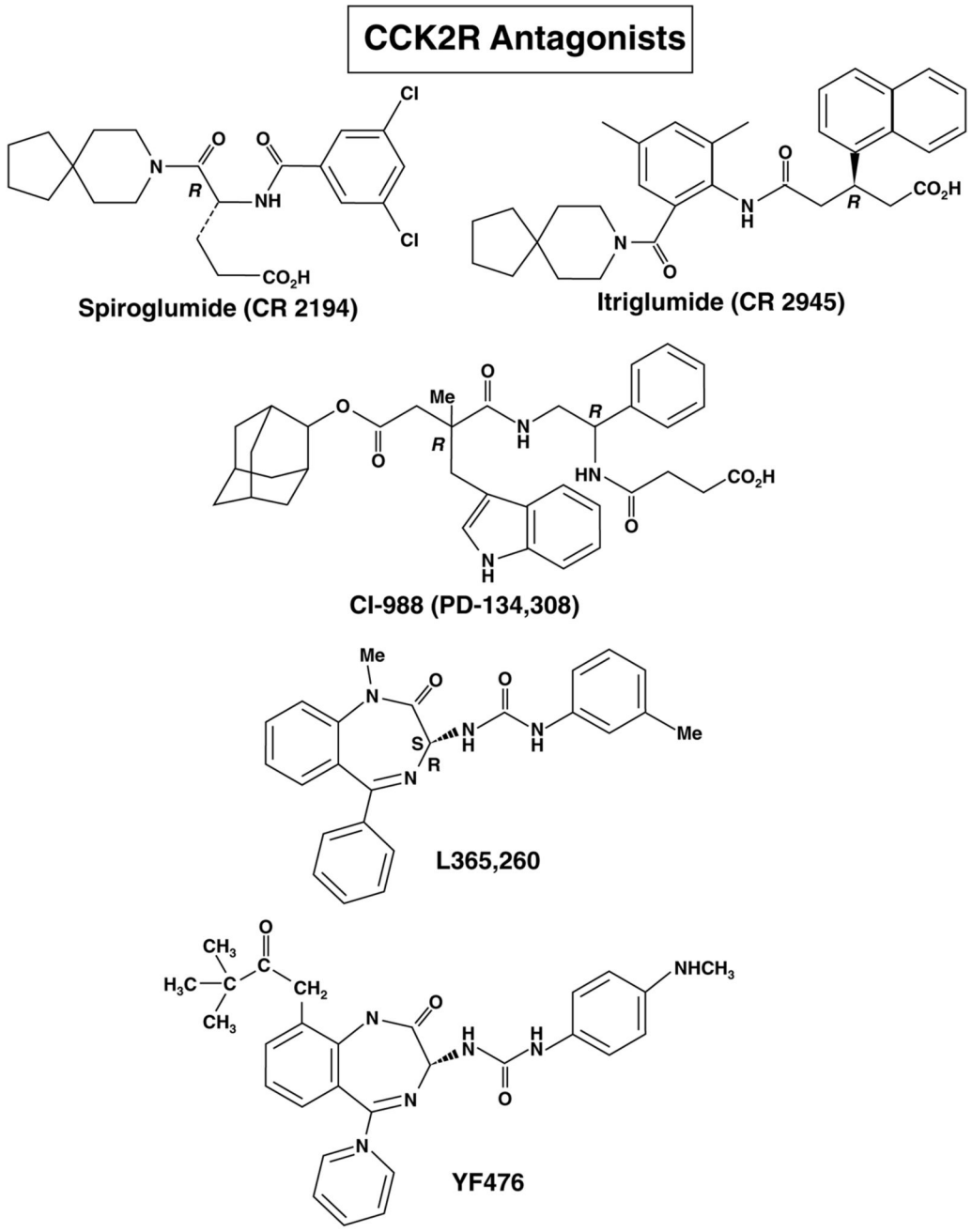

Figure 2.
Structure of CCK2 receptor antagonists used in human studies. CCK1R and CCK2R CCK1R and CCK2R affinities, chemical structures and references are listed in Table 3.

Table 1

CCK and CCK1R in the gastrointestinal tract: physiological functions and possible disorders

Physiological functions	
1.	Contraction of gallbladder/relaxation sphincter of Oddi
2.	Stimulation of pancreatic secretion
3.	Inhibit colonic motility
4.	Inhibit gastric emptying
5.	Decrease lower sphincter pressure /increase in sphincter relaxation
6.	Inhibition of acid secretion
Possible disease involvement.	
1.	CCK-deficient states (celiac sprue, bulimia, diabetes mellitus, autoimmune polyglandular syndrome-type 1)
2.	Pancreatic disorders (acute/chronic pancreatitis)
3.	GI motility disorders [gallbladder disease (cholesterol stores, acalculous cholecystitis), irritable bowel syndrome, functional dyspepsia, chronic constipation]
4.	Tumor growth
5.	Satiety disorders

Table 2

Causes of chronic hypergastrinemia

a.	**Associated with gastric acid hyposecretion-achlorhydria**	
	1.	Pernicious anemia-atrophic gastritis
	2.	Treatment with potent acid antisecretory agents (especially with H^+-K^+-ATPase inhibitors)
	3.	Chronic renal failure (common)
	4.	*H. pylori* infection
	5.	Post-gastric acid-reducing surgery
B.	**Associated with gastric acid hypersecretion**	
	H. pylori infection	
	Gastric outlet obstruction	
	Antral G-cell hyperfunction-hyperplasia	
	Chronic renal failure (rare)	
	Retained gastric antrum syndrome	
	Short-bowel syndrome	
	Gastrinoma (Zollinger-Ellison syndrome)	

Table 3

CCK1R and CCK2R Antagonist used in human studies[1]

		IC_{50} (μM)		
		CCK1R	CCK2R	Fold CCK1R preferring
CCK1R preferring				
A.	*Glutaramic acid analogues*			
	Proglumide[2]	6,000	11,000	1.8
	Lorglumide (CR 1409)[3]	0.13	300	2,300
	Loxiglumide (CR 1505)[4]	0.33	9.1	27
	Dexloxiglumide (CR 2017)[5]	0.12	22	170
B.	*1,4 Benzodiazepines*			
	L-364,718 (MK-329, Devazepide)[6]	0.08	270	3,400
C.	*Other*			
	Lintript (SI-27897)[7]	0.58	489	843
				Fold CCK2R preferring
CCK2R preferring				
A.	*Glutaramic acid analogues*			
	Spiroglumide (CR 2194)[8]	13,500	1,400	9.6
	Itriglumide (CR 2945)[9]	20,700	2.3	9,000
B.	*1.4 Benzodiazepines*			
	L-365,360[10]	280	2	140
	YF476[11]	502	0.11	5,020
C.	*Dipeptoids*			
	CI-988 (PD-134,308)[12]	4,300	1.1	2,501

[1] Data are from [6,40,47,334–338,373–375]

[2] D,L-4-benzamido-N,N-dipropyl-glutaramic acid

[3] [D, L-4-(3,4-dichlorobenzoylamino)-5-(di-N-pentylamino)-5-oxopentanoic oxid]

[4] [D, L-4+(3,4 dichlorobenzamido)-N-(3-methoxypropyl)-N-pentylglutaramic acid]

[5] [(R)-4-(3,4-dichlorobenzoylamino)-5-[N-(3-methoxylpropyl)-N-pentylamino]-5-oxopentanoic acid]

[6] [3S(−)-N(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepine-3-yl)-1H-indole-2- carboxamide]

[7] 1-([2-(4-(2-chlorophenyl)thiazole-2-yl)aminocarbonyl]indolyl) acetic acid

[8] (R)-8-Azaspiro[4,5]decaane-8-pentanoic acid

[9] (R)-1-naphtalene propionic acid

[10] 3-R(+)-(N-2,3-Dihydro-1methyl-2-oxo-5-phenyl-1 H-1,4 benzodiazepin-3-yl)-N'-(3- methylphenyl)urea

[11] ((R)-1-[2.3 dihydro-2-oxo-1-pivaloylmethyl-5-(2'pyridyl)-1H-1,4-benzodiazepin-3-yl]-3- (methylamino-phenyl)urea

[12] 4-[[2-[[3-(1H-indol-3-yl)-2-methyl-1-oxo-2[[(tricyclo[3.3[12.17]dec-2-yloxy)- carbonyl]amino]-propyl]amino]-1-phenyethyl]amino]-4-oxo-[R-(R*,R*)]-butanoate N-methyl- D-glucamine

Table 4

Gastrin and CCK2R in the gastrointestinal tract: physiological functions and possible disorders

Physiological functions		
1.	Stimulation of gastric acid secretion	
2.	Stimulation of gastric mucosa growth (esp ECL cells)	
3.	Inhibit of gastric empyting	
Possible disease involvement		
I.	*Proven:*	
		Hypergastrinemic states [physiological (atrophic gastritis, pernicious anemia), and pathological (Zollinger-Ellison syndrome)]
		Abnormalities due to gastric mucosal effects of hypergastrinemia (ECL cell hyperplasia, carcinoids, ↑ parietal cell mass)
	Acid-peptic disorders	
II.	*Possible:*	
	a. Tumor growth (colon, gastric, pancreatic, liver)	