CCK_B/Gastrin Receptor Antagonists: Recent Advances and Potential Uses in Gastric Secretory Disorders

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Cholecystokinin (CCK) and the structurally related peptide, gastrin, have numerous effects on tissues in the central nervous system and gastrointestinal tract. Recent studies show these effects are mediated by a CCK_A and CCK_B receptor. Knowledge of the physiological role and role of CCK_B receptors in pathologic processes has been particularly limited by the availability of selective, potent receptor antagonists. Recently, new members of five different classes of non-peptide CCK_B receptor antagonists are reported and are reviewed briefly. These include compounds isolated from Streptomyces (tetrothiodin, virginiamycin analogues), ureido-acetamide analogues (RP 69758, RP 72540, RP 73870), newer benzodiazipine analogues (L-368,935, L-740,093, YM022), pyrazolidimine analogues (LY 262,691) and glutamic acid analogues (CR2194). Many of these compounds have greater than 1000-fold selectivity for the CCK_B over the CCK_A receptor and some have greater than 10,000-fold selectivity. The pharmacology and effects of CCK_B receptor antagonists on gastric acid secretion is briefly reviewed. Furthermore, the possible clinical usefulness of CCK_B receptor antagonists in treating disorders of gastric acid secretion, in inhibiting the trophic effects of gastrin and in other clinical conditions is briefly discussed.

INTRODUCTION

In this article, recent advances in the identification of selective cholecystokinin B (CCK_B) (gastrin) receptor antagonists will be briefly reviewed and their possible therapeutic role in the treatment of gastric secretory disorders briefly discussed. To address these questions, it is important first to have a general understanding of the role of CCK receptors in different processes as well as to understand the recent advances in classifying receptors that mediate the action of CCK and gastrin-related peptides. These areas will be briefly reviewed first.

I. CLASSIFICATION OF CCK RECEPTORS AND THEIR ROLES IN DIFFERENT PHYSIOLOGICAL PROCESSES

Cholecystokinin (CCK) structurally closely resembles gastrin at its carboxyl terminal, which is the biological active portion of the peptide [1-7]. Both peptides end in the pentapeptide gly-trp-met-asp-phe-NH2 [2, 8]. However, they differ in the presence or absence of a sulfated tyrosine in position 7 from the carboxy-terminal phenylalanine amide. The presence of this group is the primary determinant of high affinity to cause the classical actions of CCK of stimulating pancreatic secretion and gallbladder contraction [2-5, 7, 8]. Recent studies demonstrate CCK immunoreactivity is widely distributed in the central nervous system (CNS) and gastrointestinal tract (in duodenal I cells and in nerves), whereas gastrin immunoreactivity is more localized, occurring predominantly in gastric antral and duodenal G cells, with low levels in various neuroendocrine tissues (pituitary, hypothalamus and gut).

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\(^{b}\)Abbreviations: CCK, Cholecystokinin; CNS, central nervous system; GRP, gastrin-releasing peptide; ECL, enterochromaffin cells; GERD, gastroesophageal reflux disease.
adrenal medulla, vagus), genital tract and respiratory tract [6, 9]. CCK has been shown to
have effects on many tissues including in the CNS (functioning as a neuropeptide, mod-
ulation of dopaminergic activity and opioid analgesia) [4, 10]; to have growth effects (pan-
creas, various tumor issues) [4, 6, 11]; to stimulate pancreatic secretion of water, elec-
trolytes, enzymes and insulin [4, 12-14]; to have motility effects (contraction of the gall-
bladder, intestinal smooth muscle, delay gastric emptying and colon motility) [4, 14, 15];
to have gastric secretory effects (stimulate pepsinogen release, somatostatin release from
D-cells, inhibit acid secretion) [4, 16-19]; and to stimulate peripheral neural effects
(vagally mediated satiety) [10]. Gastrin also has been shown to cause many of the changes
mediated by CCK in various tissues [10]; to have stimulatory effect on gastric acid secre-
tion, [9]; to have trophic effects on the gastric mucosa, particularly on gastric enterochro-
maffin-like cells [9]; to have growth stimulatory effects on numerous tumors [6, 9, 11];
and to have CNS effects (anxiogenic action) [4, 20].

Numerous pharmacological, biological, and now structural studies provide evidence
that two classes of CCK receptors mediate the actions of CCK and gastrin: a CCKA recep-
tor and a CCKB receptor [21-25]. The gene encoding the CCKA receptor has been cloned

| Table 1. Comparison of CCKA and CCKB receptors. |
|-----------------------------------------------|
| Structure                                    |
| CCKA receptors                               |
| CCKB receptors                               |
| 428AA (human)                                |
| 47AA (rat)                                   |
| 447AA (human)                                |
| 452AA (rat)                                  |
| Signaling pathway                            |
| PLC                                          |
| PLC                                          |
| Natural agonists                             |
| CCK-8>GCCK-4                                 |
| CCK, G17II>GCCK-4                            |
| Selective agonists                           |
| A-71378                                      |
| A72962                                       |
| SNF-8702                                     |
| Cyclic compound II                           |
| Gastrin                                      |
| Older selective antagonists                  |
| L364, 718 (devazepide)                       |
| Lrglumide (CR1409)                           |
| CI-988 (PD134, 308)                         |
| L365, 260                                    |
| Distribution                                 |
| CNS (limited), islets,                       |
| pan. acini, gallbladder                      |
| muscle, neurons (GI tract)                   |
| CNS (general), GI                            |
| Smooth muscle, Pan. acini                   |
| Gastric location                             |
| Chief cells, D cells                        |
| Chief cells (some species),                  |
| Parietal cells (dog), ECL cells (rat, dog),  |
| D cells (dog), neurons in circular muscle    |
| plexus, gastric smooth muscle                |

Abbreviations: PLC-phospholipase C; CNS-central nervous system; G17I and G17II-refer to
the nonsulfated and sulfated analogues of gastrin-17. CCK-8 and CCK-4 are the COOH terminal
octapeptide and tetrapeptide of cholecystokinin. A-71378=[des amino, Nle28, 31, N-methyl Asp32]
CCK-27-33(7); A72962=[des amino-Nle28 N-methyl-Leu31]CCK-27-33(28); SNF-8702-[N-
methyl-Nle28, 31]CCK(26-33)(30); cyclic compound II-BOC-γ-D-Glu26, Tyr(SO3H)-Ahx-DLys-
Trp-Ahx- Asp-Phe-NH₂ (Ahx=2 aminohexanoic acid) (29); L364, 718 (MK-329, devazepide)
[3S(-)-N(L2, 3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1, 4-benzodiazepin-3-yl)-1-H-ideole-2-car-
boxide. Loxiglumide (CR1409)-D, L-4-(3, 4-dichlorobenzyo amino)-5-(dipentyl amino)-5-oxo-
pentanoic acid. The structures of L-365, 260 and CI- 988 are shown in Figure 1. Data are from
References [12, 23, 25, 27, 32, 44].
from numerous species and in the human DNA sequence predicts a protein that has 428 amino acids and is a member of the G protein-coupled superfamily of receptors with seven spanning areas [21, 23] (Table 1). The CCK_{B} receptor, originally characterized best pharmacologically in the CNS, is now known to be the same as the gastrin receptor originally characterized in parietal cells [21, 23, 24, 26, 27]. The CCK_{A} receptor gene has also been cloned from numerous species and the predicted human protein has 447 amino acids, 48 percent homology with the human CCK_{A} receptor and is also a member of the G protein-coupled heptahelical superfamily [21, 23, 24, 26, 27]. The CCK_{A} receptor and CCK_{B} receptor differ from each other in their affinities for natural agonists (Table 1), distribution (Table 1), affinity for certain selective agonists (Table 1) [12, 2, 8-30] and antagonists (Tables 1 and 2). Of the many actions of CCK and gastrin on different tissues, CCK_{A}

Table 2. Affinities of recently described CCK_{B} receptor antagonists for rat CCK_{A} and CCK_{B} receptors.

| Antagonist | rCCK_{A}-R | K_{i} or IC_{50} (nM) | Fold CCK_{B}-Preferring | Ref. |
|------------|------------|----------------------|------------------------|-----|
| L-365, 260(1) | 1, 170 | 11 | 106 | [61, 47] |
| CR-2194(2) | 13, 500 | 1.00 | 23 | [64] |
| LY-262, 691(5) | 11, 500 | 31(m) | 370 | [65] |
| Tetronothiodin | >10, 000 | 3.6 | 27, 000 | [50] |
| L-156, 586(4) | >40, 000 | 90 | 444 | [50, 51] |
| CI-988 (PD-134, 308)(5) | 6, 600 | 6.3 | 1, 048 | [47, 36] |
| Benzodiazepines | YM022(6) | 63 | 0.068 | 926 | [47] |
| | L-740, 093(7) | 1, 600 | 0.10(GP) | 16, 000 | [62] |
| Ureido-acetamides | RP69758(8) | 4, 734 | 4.3 | 1, 182 | [61] |
| | RP72540(9) | 2, 756 | 1.2 | 2, 300 | [61] |
| | RP73870(10) | 1, 634(GP) | 0.48(GP) | 3, 404 | [62] |
| Acidic benzodiazepine | L-368, 935(11) | 1, 400 | 0.14(GP) | 10, 000 | [54] |

All data are affinities from binding studies using primarily ^{125}I-BH- CCK-8 and are for rat pancreas (rCCK_{A}-R), rat cortex or gastric glands (rCCK_{B}-R) except those indicated by GP which are from guinea pig and m which are from mouse.

1. L-365, 260-3R(+)-(N-2, 3-dihydro-1-methyl-2-oxo-5-phenyl-1 H-1, 4-benodiazepin-3-yl-N'(3-methylphenyl)urea.
2. CR 2194-(R)-4-(3, 5-dichlorobenzamido)-5-(8-azaspiro-[4.5]decan-8-yl)-5-oxo-pentanoic acid. [64].
3. LY-262, 691-1-(4-bromophenylaminocarbonyl)-4, 5-diphenyl-3-pyrazolidinone [65].
4. L-156, 586 15-dihydro-13, 14-anhydro-virginamycin M1 [51].
5. CI-988-4-[2-{3-(1H-indol-3-yl)-2-methyl-1-oxo-2[[tricyclo[3.3.12,17]dec-2-yloxy]-carbonyl]-amino}-propyl]-amino]-1-phenethylaminol-4-oxo-[R-(R*, R*)]-butanoate N-methyl-D-glucamine [36]
6. YM022 (R)-1-[2, 3-dihydro-1-(2'-methylphenacyl)-2-oxo-5-phenyl-1H-1, 4-benodiazepin-3-yl]-3-(methylphenyl)urea. [47].
7. L-740, 093-[N-{(3R)-5-(3-azabicyclo[3.2.2]nonan-3-yl)-2, 3-dihydro-1-methyl-2-oxo-1H-1, 4-benzodiazepin-3-yl}-N'-(3-methylphenyl)urea] [57].
8. RP 69, 758-(3-[3-N-(N-methyl N-phenyl-carbamoylmethyl)N-phenyl-carbamoylmethyl]ureido)phenylacetic acid [61].
9. RP 72540 (RS)-3-[3-N-(3-methoxy-phenyl) N-(N-methyl N-phenyl-carbamoylmethyl)carbamoyl]ureido]phenylpropionic acid [61].
10. RP 73870 ((N-{methoxy-3-phenyl}-N-(N-methyl-N-phenyl-carbamoylmethyl)-carbamoylmethyl]-3-ureido)-3-phenyl]-2-ethylsulfonate-(RS) [62].
11. L-368, 935 (N-1, 3-dihydro-1(2-methyl)propyl-2-oxo-5-phenyl-1H-1, 4-benzodiazepin-3-yl)-N-(3-(1H-tetrazol-5-yl)phenyl)urea) [54].
receptors [4, 9, 23] are thought to mediate CCK-stimulated pancreatic enzyme, electrolyte and insulin secretion; pancreatic growth, gastric effects (pepsin release, acid inhibition, somatostatin release from D-cells); motility effects (decreased gastric and colonic motility); gallbladder effects (contraction of gallbladder and relaxation of the sphincter of Oddi); and some CNS or neural effects (satiety, opioid and analgesic effects). CCKB receptors are thought to mediate stimulation of gastric acid secretion, trophic effects on ECL cells and gastric mucosa and some CNS effects (anxiety attacks). Which of these actions are pharmacological and which are physiological are at present unclear in most cases. Furthermore, because CCK can interact with high affinity with both CCKA and CCKB receptors [4, 23, 25, 31], in many cases, whether CCKA or CCKB receptors mediate many actions of CCK remains unclear. Only with the recent availability of selective antagonists will this become clear.

II. RECENT ADVANCES IN THE DEVELOPMENT OF POTENT, SPECIFIC CCKB RECEPTOR ANTAGONISTS

Until recently, CCK receptor antagonists with only limited selectivity for CCKB receptors existed [32]. Whereas the benzodiazepine analogue, L-364, 718, and the progilumide analogue, iorglumide (CR 1409), or the closely related compound, loxiglumide (CR 1505), have proven to have sufficient selectivity for CCKA receptors both in vitro and in vivo to define the role of CCKA receptors in various processes, this has not been the case with the selective CCKB receptor antagonists benzodiazepine analogue, L-365, 260 or the dipeptoid compound, CI-988 (PD 134, 308) (Table 1). The use of L-365, 260 has been limited by its relatively low selectivity and also its use has been limited in dogs by a reversal of the affinities of L-364, 718 and L-365, 260 for CCKB receptors, as well as the low selectivity of both antagonists in this species [21, 26, 33]. A recent study demonstrates that the difference in selectivity of L-365, 260 and L-364, 718 for human and rat CCKB receptors compared to canine CCKB receptors is due primarily to the substitution of leucine in the canine CCKB receptor for valine in the equivalent position (valine) in the 6th transmembrane region of the human CCKB receptor [26, 33]. Although CI-988 (PD 134, 308) has more than 1000-fold selectivity for CCKB receptors over CCKA receptors (Table 2), its general usefulness has been limited by recent reports that this compound has agonist activity in some systems. PD-136, 450 (also called Cam-1189) is a dipeptoid analogue closely related to PD-134, 308, and it has been shown recently to function as a partial CCKB Receptor agonist in the rat stomach for acid secretion [34], and as a full agonist at CCKA receptor for stimulating pancreatic enzyme secretion in rats [34, 35]. Furthermore, PD-135, 158, which is also closely related to PD-134, 508 [36], also functions as a CCKA receptor agonist in rat pancreatic acini [37]. Recent studies have demonstrated marked species differences in agonist/antagonist activity of various classes of peptide antagonists to other receptors. For example, various classes of peptide antagonists of the gastrin peptide-releasing receptors such as bombesin pseudopeptides, des Met14 bombesin amides and alkyl amides are excellent gastrin-releasing peptide (GRP) receptor antagonists in mouse and guinea pig but function as GRP receptor agonists or partial agonists in rats [38-40]. Similarly, chimeric galanin peptide receptor antagonists such as galantide [41] and CCK peptide analogues such as CCK-(26-32)NH2, function as agonists, partial agonists and antagonists in different species [42]. These data suggest that mixed agonist/antagonist activity in different species or cell systems may be a general property of many peptide analogues that function as antagonists in some assays.

Recently, a number of different classes of highly selective non-peptide CCKB receptor antagonists have been described (Table 2, Figure 1). Some of these compounds have >2000-fold selectivity for CCKB receptors (Table 2, Figure 1) compared to L-365, 260.
Figure 1. Structure of newer CCKB receptor antagonists. The A/B ratio refers to the relative affinity of the indicated compound for rat CCKA receptors compared to its affinity for rat CCKB receptors. Numbers greater than 1 indicate the number of times the compound is selectivity for CCKB over CCKA receptors. Ratios are calculated from the affinities listed in Table 2. The structures of four different classes of CCKB receptor antagonists are shown. Shown are the benzodiazepine analogues related to the prototype compound L-365, 260 which include L-740, 073, YM022, L-368, 935, the natural occurring compound, tetronothiodin isolated from Streptomyces, the dipeptoid analogue CI- 988 and the ureido-acetamide analogue RP-72540.

which has a selectivity of 80-280-fold for the CCKB over the CCKA receptor in different species (Table 1) and a five- to 180-fold selectivity in human transfected CCK receptors [21, 23, 43-47]. In general, the new CCKB receptor antagonists fall into five different chemical groups: tetronothiodin and other compounds isolated from Streptomyces, ureido-acetamide analogues, benzodiazepine analogues, glutamic acid analogues or proglumide analogues, and pyrazolidinone analogues.
Tetronothiodin has a 19-membered ring with an alpha-acyltetronic acid and a tetrahydrothiophene moiety (Figure 1) and was isolated from the culture broth of *Streptomyces* sp. NR0489 [48, 49]. Tetronothiodin is completely different structurally from any of the other CCK<sub>β</sub> receptor antagonists (Figure 1) including the virginiamycin analogues L-156, 586, L-156, 587 and L-156, 588, which were also selective CCK<sub>β</sub> antagonists and were isolated from *Streptomyces olivaceus* [49-51] and from asperlicin, a CCK<sub>A</sub> receptor antagonist isolated from *Aspergillus alliaceus* [52]. A recent study [50] reports that while tetronothiodin has high affinity (affinity constant [K<sub>i</sub>] = 3.6 nM) for CCK<sub>β</sub> receptors in the rat and a 27, 000 selectivity for rat CCK<sub>β</sub> over rat CCK<sub>A</sub> receptors (Table 2), it has a 80-fold (K<sub>i</sub> = 280 nM) and 60-fold (K<sub>i</sub> = 210 nM) lower affinity for mouse and human CCK<sub>β</sub> receptors (cerebral cortex) than for rat CCK<sub>β</sub> receptors. Tetronothiodin functions as a selective CCK<sub>β</sub> receptor competitive antagonist in the rat [50, 53], however its lower affinity may limit its usefulness in humans and mice.

The newer benzodiazepine CCK<sub>β</sub> receptor antagonists include various 1, 4-benzodiazepine derivatives including ones containing an acidic group on the phenylurea portion of L-365, 260 (Figure 1), such as the tetrazole derivative L-368, 935 [54, 55] (Figure 1). L-368, 935 has much greater water solubility than L-365, 260, very high selectivity for CCK<sub>β</sub> receptors (Table 2) and also has high affinity for human CCK<sub>β</sub> receptors (K<sub>i</sub> = 27 nM) [54]. L-368, 935 is active in vivo blocking pentagastrin-stimulated acid secretion in rats with an ED<sub>50</sub> of 0.14 mg/Kg [intraperitoneal (i.p.)], compared to an ED<sub>50</sub> of 0.83 mg/Kg for L-365, 260 (i.p.) [54, 55]. Using an ex vivo binding model in the mouse brain and other studies, it was demonstrated this compound does penetrate the CNS, although to a lesser extent than L-365, 260 [54, 55]. To improve the brain penetration, a series of amidine 5-amino-1, 4-benzodiazepine analogues which had an amine-based cationic group within the benzodiazepine moiety were synthesized [56, 57] and the azabicyclo-nanane derivative L-740, 093 was identified and fully characterized [56, 57] (Figure 1). L-740, 093 has a very high affinity for guinea pig CCK<sub>β</sub> receptors (concentration causing half-maximal inhibition, [IC<sub>50</sub>] = 0.10 nM) and a 16, 000-fold selectivity for CCK<sub>β</sub> over CCK<sub>A</sub> receptors (Table 2). L-740, 093 blocks pentagastrin-induced gastric acid secretion with an ED<sub>50</sub> of 0.01 mg/Kg which is 100-times more potent than L-365, 260. L-740, 093 has a much greater water solubility than L-365, 260 and also has greater than 60-increased activity in the ex vivo brain binding assay, suggesting much greater CNS penetration [56-58]. The 5-phenyl-1, 4-benzodiazepine analogue, YM022, is also a potent CCK<sub>β</sub> receptor antagonist in the rat (K<sub>i</sub> = 0.068 nM) (Table 2) and has greater than 100-fold selectivity for CCK<sub>β</sub> over CCK<sub>A</sub> receptors [47, 59]. Administration of YM022 inhibited pentagastrin-induced gastric acid secretion with an ED<sub>50</sub> of 0.0078 μM/Kg and was 540-fold and 129-fold more potent than L-365, 260 (concentration causing half-maximal stimulation [EC<sub>50</sub>] = 4.23 μMol/Kg) and CI-988 (EC<sub>50</sub> = 1.01 μMol/Kg), respectively [47]. In contrast to L-365, 260, neither YM022 nor CI-988 inhibited histamine or bethachol-stimulated acid secretion, whereas L-365, 260 inhibited both [47]. YM022 orally dose-dependently inhibited acid secretion in pylorus-ligated rats with an ED<sub>50</sub> of 0.83 μMol/Kg compared to 1.6 μMol/Kg for famotidine and 10.9 μMol/Kg for omeprazole [59]. In rats, YM022 is as potent as famotidine at preventing in rats indomethacin-induced gastric lesions, gastric damage caused by water-immersion and restraint, gastric erosions caused by acidified ethanol and meperiozole-induced duodenal ulcers [59]. Recently, a series of imidazo 1, 4-benzodiazepine analogues have been reported [60]. Compound 12 in this series (N-[2S, 4R]-methyl- 6-phenyl-2, 4-dihydro-1H-imidazol-2-yl]-N-[3-methyl phenyl]-urea) was selected as the prototype compound having a high affinity for CCK<sub>β</sub> receptors on guinea pig cortical membranes (IC<sub>50</sub> = 0.06 nM) and low affinity for
rat pancreatic CCK$_A$ receptors (IC$_{50}$ =130 nM), thus having a 2160-fold selectivity for CCK$_B$ receptors [60]. This compound has similar CNS penetration to L-365, 260 [60].

The ureido-acetamide analogues RP 69758, RP 72540, and RP 73870 are reported to be potent and selective CCK$_B$ receptor antagonists (Table 2, Figure 1) [61-63]. Each of these analogues has greater than 1000-fold selectivity for CCK$_B$ receptors over CCK$_A$ receptors with RP 73870 having greater than 3000-fold selectivity (Table 2). Each of these compounds inhibits pentagastrin-stimulated acid secretion [61, 62], with RP 73870 causing half-maximal inhibition at 0.05 mg/Kg, i.v.) and was two-fold less potent than famotidine, nine-fold more potent than CI-988, 26-fold more potent than cimetidine and 40-fold more potent than L-365, 260 [62]. RP 73870, at a concentration sufficient to block pentagastrin-stimulated secretion (0.3 mg/Kg, i.v.) has no effect on histamine-stimulated acid secretion, whereas famotidine is equally potent for both [62]. RP 73870 prevents aspirin-induced gastric mucosal injury and is about one-half as potent as cimetidine and 3.5-times as potent as L-365, 260 [62]. RP 73870 also prevents cysteamine-induced duodenal ulceration when given orally and is as potent as omeprazole or famotidine and six-fold more potent than L-365, 260 [62].

Two other classes of selective CCK$_B$ receptor antagonists are described (Table 2). Various glutaric acid derivatives are recently described that have a higher affinity for the CCK$_B$ than the CCK$_A$ receptor such as CR 2194 (Table 2) [64]. From binding studies, CR 2194 only has a 23-fold selectivity [64], for CCK$_B$ receptors, however, it inhibits pentagastrin-stimulated acid secretion in the dog, rat and cat [64]. A number of pyrazolidinone analogues are CCK$_B$ selective antagonists [65, 66]. One of the most potent, LY 262, 691 (Table 2), inhibits CCK-8-induced depolarization in ventromedial hypothalamic neurons and causes a specific decrease in the number of spontaneously active dopamine cells in the central segmental area, whereas CCK$_A$ receptor antagonists have no effect [65, 66]. This latter compound has a 370-fold selectivity for CCK$_B$ over CCK$_A$ receptors, which is considerably less than the newer benzodiazepine analogues and the ureido-acetamide analogues (Table 2).

III. CCK$_B$ RECEPTOR-MEDIATED GASTRIC CHANGES IN WHICH ANTAGONISTS MIGHT BE THERAPEUTICALLY USEFUL

Before the possible therapeutic uses of CCK$_B$ receptor antagonists in gastric secretory disorders is considered, it is important to understand what is known about the location and function of CCK$_B$ gastrin receptors in the stomach. Limited data are available. Because of the difficulty of purifying each cell type, the exact location of CCK$_B$ receptors in the stomach has only been determined in a few cell types. In the stomach, binding and/or functional studies provide evidence for CCK$_A$ receptors on human [67], guinea pig [18, 68] and rat chief cells [17, 69], whereas both CCK$_A$ and CCK$_B$ receptors are on guinea pig chief cells [18, 68, 70, 71] (Table 1). Both CCK$_A$ and CCK$_B$ receptors exist on canine D cells and regulate somatostatin release [72]. CCK$_B$ receptors are found in canine parietal cells [73], enterochromaffin cells (ECL cells) in dog and rat [74, 75], and reported to be present in both neurons in the gastric circular muscle layer and in the myenteric plexus in the stomach [76]. Pharmacological studies and binding studies provide evidence for CCK$_B$ receptors on gastric smooth muscle [77, 78] (Table 1).

Evidence exists that activation of CCK$_B$ receptors in the stomach can stimulate acid secretion [9, 79, 80]; release histamine from ECL cells in rat and dog [74, 75, 81]; stimulate growth of the mucosa of the oxyntic gland area of the stomach increasing mucosal weight, RNA, protein synthesis, and DNA synthesis [9, 79, 82]; stimulate ECL proliferation [83, 84], stimulate somatostatin secretion in in vitro preparations [72]; increase gastric blood flow; increase pepsinogen secretion in some species and alter gastric motility [9, 79, 80]. The responses that are thought physiological are the trophic effects [9, 79],
effects on histamine release, acid secretion and perhaps effects on blood flow. For CCK\textsubscript{B} receptor antagonists to be useful they need to inhibit one of these functions.

**IV. POSSIBLE USE OF CCK\textsubscript{B} RECEPTOR ANTAGONISTS FOR INHIBITING ACID SECRETION**

As reviewed above, it is well established that various classes of the newer CCK\textsubscript{B} receptor antagonists, as well as L-365, 260, can inhibit acid secretion in animals [47, 57, 59, 61, 62, 85]. The only specific CCK\textsubscript{B} receptor antagonist examined in humans on acid secretion is L-365, 260 [86]. In this study [86], in eight healthy male volunteers, oral L-365, 260 caused a dose-dependent inhibition of pentagastrin-stimulated acid secretion, with the 50 mg dose causing half-maximal inhibition. In this study [86], it was estimated that 50 mg of L-365, 260 caused acid inhibition equal to that caused by five mg of famotidine. It was concluded that the acid inhibitory effect of L-365, 260 was modest and of relatively short duration and, therefore, was unlikely to be clinically useful for this purpose [86]. Furthermore, in many animal studies the CCK\textsubscript{B} receptor antagonists are much more potent at inhibiting pentagastrin-stimulated acid secretion rather than that caused by histamine or cholinergic agents, demonstrating the specificity of its action for the CCK\textsubscript{B} receptor [47, 62]. This is in contrast to histamine H\textsubscript{2}-receptor antagonists or H\textsuperscript{+}-K\textsuperscript{+} ATPase inhibitors, which inhibit acid secretion stimulated by all secretagogues. Each of these latter compounds inhibit acid secretion by all stimulus: the H\textsuperscript{+}-K\textsuperscript{+} ATPase inhibitors because of inhibiting a common late step in acid secretion, and histamine H\textsubscript{2}-receptor antagonists by inhibiting the action of histamine which plays a critical pivotal role in acid secretion mediated by all stimuli [81]. These results suggest that even if a potent, long-acting CCK\textsubscript{B} antagonist is developed that causes prolonged inhibition of pentagastrin-stimulated acid secretion, because of the specificity of its action for gastrin-stimulated secretion, it is likely to be less useful than the H\textsuperscript{+}-K\textsuperscript{+} ATPase inhibitors or histamine H\textsubscript{2}-blockers.

It could be argued that CCK\textsubscript{B} receptor antagonists might be particularly useful for hypergastrinemic states associated with acid hypersecretion such as Zollinger-Ellison syndrome or antral G cell hyperfunction/hyperplasia [87, 88]. However, the H\textsuperscript{+}-K\textsuperscript{+} ATPase inhibitors are highly effective in these cases, controlling acid hypersecretion with once or twice a day dosing [88, 89] and for the few patients who can not take these agents, histamine H\textsubscript{2}-receptor antagonists are effective [88, 89]. It is unlikely CCK\textsubscript{B} receptor antagonists could improve on the acid-inhibitory effects offered by these agents even in hypergastrinemic states, however it may have a use because of the trophic effects of gastrin in these conditions as discussed below.

**V. POSSIBLE USE OF CCK\textsubscript{B} RECEPTOR ANTAGONISTS FOR INHIBITING THE TROPIC EFFECTS OF HYPERGASTRINEMIA**

Recently, there has been increased concern about the consequences of prolonged hypergastrinemia [87, 90-92]. This has occurred because moderate to severe gastroesophageal reflux disease (GERD) is not uncommon and the H\textsuperscript{+}-K\textsuperscript{+} ATPase inhibitors are the most effective agents for treatment of GERD of this severity [93]. The chronic use of H\textsuperscript{+}-K\textsuperscript{+} ATPase inhibitors for GERD and occasionally for peptic disease causes hypergastrinemia in 80 to 100 percent of patients [94, 95] with 30 percent of patients in one study [94] having serum gastrin concentrations more than five-times the upper limit of normal. It is well established that chronic hypergastrinemia causes an increased rate of the development of gastric carcinoid tumors in animals and man, some of which are malignant [83, 84, 90, 96, 97]. Furthermore, it is controversial whether chronic hypergastrinemia increases the risk of development or growth of colonic neoplasms [90, 98-101].
Therefore, the possible use of a CCK\textsubscript{B} receptor antagonist in chronic gastroesophageal reflux disease might both control gastric acid hypersecretion and also inhibit the possible trophic effects of the chronic hypergastrinemia. While theoretically attractive, with the currently available information, it seems unlikely that CCK\textsubscript{B} receptor antagonists will be useful for this purpose for a number of reasons. First, profound, prolonged inhibition of gastric acid hypersecretion is needed to control symptoms and heal the mucosal lesions in many patients with moderate to severe GERD. The H\textsuperscript{+}-K\textsuperscript{+} ATPase inhibitors have proven effective at accomplishing this and also have proven safe except for the risk of hypergastrinemia. Patients with acid hypersecretory disorders have been treated with omeprazole for 10 years and patients with idiopathic GERD up to seven years without drug-induced side-effects [94, 95, 102]. The CCK\textsubscript{B} receptor inhibitors developed so far do not cause profound, prolonged inhibition of acid secretion, with L-365, 260 having only a modest inhibition (50 mg orally equal to five mg famotidine), and the effect was short-lived [86]. Secondly, CCK\textsubscript{B} antagonists are much more effective against gastrin-stimulated secretion and have minimal effects on histamine or cholinergic-stimulated secretion [47, 62]. This would suggest that their ability of CCK\textsubscript{B} receptor antagonists to inhibit all forms of acid secretion may be limited and, therefore, they would not cause the profound, prolonged inhibition required to control GERD symptoms in patients with moderate to severe disease. Lastly, in patients with idiopathic GERD or severe acid-peptic disease, treatment for up to seven years with daily omeprazole resulted in a doubling of the mean argyrophil cell count, a decrease in the percentage of patients with a normal endocrine growth pattern, an increase in the percentage of patients with micronodular hyperplasia, but no dysplastic lesions and no carcinoid tumors [95]. It was concluded [95] that omeprazole is very likely safe for up to five years of continuous treatment in terms of gastric changes. Even patients with Zollinger-Ellison syndrome with profound chronic hypergastrinemia for 10 years have a very low rate of developing gastric carcinoid tumors (0 percent in one study [103] and 0.6 percent in another study [87]). These data suggest the risk of developing significant gastric mucosal changes due to even profound hypergastrinemia is low with existing drugs for at least a five to 10-year period. Because the existing acid antisecretory drugs are so effective, safe, and even with long-term treatment the risk of chronic hypergastrinemia in terms of gastric mucosal changes is low, at present there is little evidence to suggest that the routine use of a CCK\textsubscript{B} receptor antagonist would be justified.

VI. POSSIBLE NONSECRETORY CLINICAL USES OF CCK\textsubscript{B} RECEPTOR ANTAGONISTS

One of the main potential clinical uses of these agents might be in as a drug to prevent panic attacks. These attacks are manifested as episodes of intense anxiety or fear associated with cognitive and somatic symptoms. Repeated occurrence of panic attacks occurs in two percent of the general population [104]. Familial and twin studies suggest in some cases the disorder is inherited [104]. CCK\textsubscript{B} receptor agonists can precipitate these attacks and CCK\textsubscript{B} receptor antagonists can prevent the attacks [104-106]. However, in a recent placebo-controlled trial [40, 43], 88 patients with panic attacks were treated for six weeks, with placebo or the CCK\textsubscript{B} receptor antagonist, L-365, 260 (30 mg, four times a day), and the results demonstrated no difference in the occurrence of the panic attacks for the two groups.

Numerous studies show gastrin can effect GI motility and CCK\textsubscript{B} receptors are known to be present on smooth muscle cells of the GI tract [77, 79]. Also, gastrin-related peptides have growth effects on a number of different tumors [98, 100, 101]. However, the exact pathogenesis of gastrin in either motility disorders or as an anticancer agent has not
been defined, and it remains unclear whether CCK<sub>B</sub> receptor antagonists could be useful clinically in these disorders.

VII. CONCLUSIONS

The recent development of five different classes of CCK<sub>B</sub> receptor antagonists that have a high selectivity and high affinity for CCK<sub>B</sub> receptor antagonists will provide important tools that will allow the role of these receptors to be defined in normal physiology and in disease states. Because most non-peptide receptor antagonists of various receptors tend not to have species-related agonist activity seen with some peptide antagonists [38, 40], these new non-peptide CCK<sub>B</sub> receptor antagonists should be generally useful because they will likely function as antagonists without agonist activity in man and other species. In which disease states CCK<sub>B</sub> receptor antagonists may be useful therapeutically is at present unclear. Because a number of classes of potent, orally active, selective inhibitors of acid secretion are currently widely used (histamine H<sub>2</sub> receptor antagonists, H<sup>+</sup>-K<sup>+</sup> ATPase inhibitors), and because of the modest effects of CCK<sub>B</sub> receptor antagonists in inhibition of acid secretion, the CCK<sub>B</sub> receptor antagonists will unlikely be therapeutically useful in this role. It is more likely they will therapeutically useful for certain CNS actions of CCK such as its ability to induce panic attacks or possibly as an antiproliferative agent.

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