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Progress in developing cholecystokinin (CCK)/gastrin receptor ligands which have therapeutic potential

Marc J. Berna^{1,3}, Jose A. Tapia^{2,3}, Veronica Sancho³, and Robert T. Jensen³

¹Department for Internal Medicine I, University Hospital Hamburg-Eppendorf, Hamburg, Germany

²Departamento de Fisiología, Universidad de Extremadura, Cáceres, 10071, Spain ³Digestive Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland

Summary

Gastrin and CCK are two of the oldest hormones and within the last 15 years there has been an exponential increase in knowledge of their pharmacology, cell biology, receptors (CCK1R, CCK2R) and roles in physiology and pathological conditions. Despite these advances there is no approved disease indication for CCK receptor antagonists and only minor use of agonists. In this review the important factors determining this slow therapeutic development are reviewed. To assess this it is necessary to briefly review what is known about the roles of CCK receptors (CCK1R, CCK2R) in normal human physiology, their role in pathologic conditions, the selectivity of available potent CCKR agonists/antagonists as well as review their use in human conditions to date and the results. Despite extensive studies in animals and some in humans, recent studies suggest that monotherapy with CCK1R agonists will not be effective in obesity, nor CCK2R antagonists in panic disorders or CCK2R antagonists to inhibit growth of pancreatic cancer. Areas that require more study include the use of CCK2R agonists for imaging tumors and radiotherapy, CCK2R antagonists in hypergastrinemic states especially with long term PPI use and for potentiation of analgesia as well as use of CCK1R antagonists for a number of gastrointestinal disorders [motility disorders (irritable bowel syndrome, dyspepsia, constipation) and pancreatitis (acute, chronic)].

Introduction

The purpose of this article is to review progress in developing cholecystokinin (CCK)/gastrin receptor ligands which have therapeutic potential. To evaluate this question it is important to have some understanding of the role of these peptides and their receptors in normal physiology, human disease states (Table 1), the availability of possible therapeutic ligands (Tables 2,3) and the results of their use in humans either to evaluate normal physiology or in human disease states. Therefore, these areas will first be reviewed briefly. With this perspective, present and future potential therapeutic uses of these ligands can be considered.

This chapter will not include a detailed discussion of a number of related areas, which have been recently reviewed. Covered in such reviews (see references below) and not reviewed here include the chemistry of the development of CCK/gastrin receptor antagonists (see [1•,2,

Correspondence to: Dr. R.T. Jensen, Building 10, Room 9C-103, National Institutes of Health, Bethesda, MD 20892-1804, Phone: 301-496-4201, Fax: 301-402-0600, E-Mail: robertj@bdg10.niddk.nih.gov.

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3••,4,5•,6•,7]) or agonists [2,5•,6•,8••,9] as well as a detailed discussion of the different chemical classes developed; detailed discussion of the biology of CCK [10,11••,12], gastrin [11••,12,13] or their receptors [11••] or detailed discussion of the studies that identified different potential disease states, especially in gastrointestinal (GI) disorders [2,3••,14•,15•].

CCK/gastrin and their receptors and normal physiology

Although gastrin was described in 1905 and CCK in 1928 making them two of the oldest known hormones, it is primarily within the last 15 years that major advances have been made. With the development of selective agonists and antagonists (Table 2,3) [1••,2,3••,4,5•,6•,7], their use in pharmacological, physiological and pathophysiological studies, and molecular characterization of the receptors and application of molecular techniques to studies, there has been major insights into the biology and physiology of these peptides, especially in humans and human disorders [3••,10,11••,12].

Pharmacological and molecular biology studies demonstrate that only two classes of receptors, a CCK1R (previously called CCK or CCKA receptor) and a CCK2R (also called gastrin or CCKB receptor) mediate the actions of CCK and gastrin [11••]. The CCK1R has high affinity for CCK and related peptides that are sulfated on a tyrosine in the 7th position from the COOH terminus with a low affinity for gastrin, whereas the CCK2R has a high affinity for both gastrin and its COOH amidated analogues longer than the tetrapeptide, as well as CCK [11••]. These receptors share 48% homology and are both widely distributed especially in the CNS and gastrointestinal tract [3••,11••].

In humans, the results of numerous studies support a role for CCK1R in regulation of a variety of physiological processes including gallbladder contraction, sphincter of Oddi relaxation, stimulation of pancreatic secretion, inhibition of acid secretion, relaxation of lower esophageal sphincter tone, slowing of colonic motility and regulation of satiety [3••,14•,15•,16]. The role of CCK1R in mediating human CNS processes remains unclear, but results primarily from animal studies suggest CCK1R activation is important in the regulation of nociception [17–19] and memory/learning [18,20]. In humans gastrin stimulates gastric acid secretion and gastric mucosal growth, especially of the gastric enterochromaffin-like cells [ECL cells] [3••,11••,12,13,15•,21,22]. Studies in genetically modified mice suggest that inhibition of gastric emptying might be a physiological function of gastrin [23], and studies in the CNS provide evidence that CCK2R are important in the regulation of memory/learning [20,24] and stress responses [24,25].

CCK/gastrin and their receptors and diseases (Table 1)

A large number of studies primarily in animals provide evidence that CCK1Rs are likely to be involved in various pancreatic disorders (acute, chronic pancreatitis), GI motility disorders (including functional dyspepsia, irritable bowel syndrome, chronic constipation, gastroesophageal reflux disease), appetite/satiety regulation and disorders (obesity, bulimia, anorexia nervosa), pain modulation and possibly regulation of tumor growth [3••,14•,15•].

Both animal and human studies demonstrate the importance of CCK2R activation in various hypergastrinemic states [3••,15•,21,22]. These including physiological hypergastrinemia resulting from atrophic gastritis, pernicious anemia, *H. pylori* infection or profound acid inhibition due to potent antiseecretory drugs such as proton pump inhibitors (PPI), as well as pathological hypergastrinemia resulting from the autonomous release of gastrin by a neuroendocrine tumor (gastrinoma) [3••,15•,21,26]. The hypergastrinemia results in stimulation of gastric ECL cells which can result in hyperplasia, dysplasia and finally gastric carcinoid tumors [15•,21,27]. Gastric carcinoid tumors are a concern because a small proportion (2–5%) of those occurring in patients with atrophic gastritis (Type 1) are malignant,

and 10–30% are malignant in patients with gastrinomas as part of the autosomal dominant syndrome, Multiple Endocrine Neoplasia type 1 (MEN1) (Type 2) [27]. Recently increased attention has been paid to the effects of chronic hypergastrinemia on gastric ECL hyperplasia in man because of the increased long-term use of potent acid suppressants such as PPIs in patients with gastroesophageal reflux disease (GERD) [3•,21,22,28]. Many of these patients can not stop taking these drugs because the GERD symptoms rapidly return. The long-term use of these drugs results in hypergastrinemia in 80–100% of patients and in 20–30% the fasting gastrin concentrations reach the range commonly seen in patients with gastrinomas [3•,21]. Long-term studies in patients with gastrinomas without MEN1 demonstrate the risk of a developing carcinoid tumor over a 10 year period was very low, but it is unknown what it may be with longer treatment and longer periods of hypergastrinemia, and therefore a number of investigators have emphasized the importance of long term surveillance in these patients [3•,21,28]. Furthermore, some investigators have raised concern about the ECL hyperplasia developing because of the long term hypergastrinemia contributing to the development of acid rebound, making it difficult to withdraw the PPIs [15•,21,22,29].

Numerous studies demonstrate that the CCK2R plays an important role in peptic ulcer disease. Acid secretion is essential for the development of peptic ulcers and gastrin is the major hormonal mediator of the gastric phase of acid secretion [15•,25,30•]. Gastrin also has a trophic effect on the parietal cells, which secrete acid, and the parietal cell mass correlates with maximal acid secretory rate [15•,30•]. Patients with *H. pylori*, the most common cause of duodenal ulcer disease, frequently have alterations in gastrin release and it has been proposed these alterations can explain most of the acid secretory abnormalities seen in patients with *H. pylori* infections [15•,31].

In addition to its growth effects on the gastric mucosa cells, numerous studies *in vitro* and in animals demonstrate that gastrin and/or its processing intermediates, and to a lesser extent, CCK, can have growth effects on human tumors [3•,15•,32•,33]. In many of these tumors the gastrin-related peptide's growth effects are mediated by CCK2R [3•,15•,32•,33]. Numerous studies demonstrate that, like to a number of other G-protein coupled receptors, human tumors frequently overexpress or ectopically express CCK2R and to a lesser extent, CCK1R [3•,32•,34•,35]. High densities or high frequency of CCK2Rs are reported on medullary thyroid cancers (MTC) (90%), insulinomas (95%), small cell lung cancers, bronchial and ileal carcinoids, GIST tumors, leiomyosarcomas and granulosa cell tumors (60–75%), and CCK1Rs in leiomyosarcomas, ileal carcinoids ((40%), meningiomas (30%) and bronchial carcinoids (20%) [34•].

The tumor growth effect of gastrin and CCK has received increased attention because of the potential therapeutic indications and the CCK2R and CCK1R overexpression because of the possibility of using this for tumor imaging or as a means of delivering CCK-receptor mediated cytotoxic agents to the tumors [3•,32•,34•,36,37]. These latter possibilities are being actively investigated because of recent results from such studies in human tumors with radiolabeled somatostatin analogues. Most human neuroendocrine tumors (carcinoids, pancreatic endocrine tumors, neuroblastomas, pituitary) as well as a number of other human tumors (CNS [meningiomas, astrocytomas], lung, breast, prostate, cancer, lymphomas) overexpress or ectopically express somatostatin receptors and this has been used extensively in clinical practice to image the location and extent of these tumors using radiolabeled somatostatin analogues [38,39]. Furthermore, recently this overexpression has been used for effective treatment of patients with advanced metastatic disease from malignant neuroendocrine tumors using ¹¹¹Indium-, ⁹⁰Yttrium- or ¹⁷⁷Lutetium-labeled somatostatin analogues [36,38,40].

Selective CCK1R and CCK2R agonists and antagonists (Tables 2,3)

To explore the role of CCK1R or CCK2R in the above diseases or in physiological states selective ligands are needed, either selective agonists or antagonists. There have been numerous classes of CCK1R and CCK2R agonists [2,5•,6•,8•,9] and antagonists [1•,2,3•,4,5•,6,41] described and in many classes, highly selective members have been reported. Table 2 summarizes a number of CCK receptor agonists or antagonists which have been used in human diseases or physiological studies and Table 3 summarizes highly selected members described in different classes that have not been used in human diseases or for human physiological studies. Historically, the selective agonists were peptides; however, recently nonpeptide 1,5-benzodiazepine analogues (GI118177X, GW 5823) and thiazole derivative SR 14613 have been described which function as CCK1R preferring agonists (Tables 2,3). Although peptide antagonists of CCK1R and CCK2R have been described [42–44] they are generally not very potent and all of the different classes of highly selective antagonists describe in Tables 2 and 3 are nonpeptide or peptoid antagonists.

As is apparent from reviewing the different agonists and antagonists in Tables 2 and 3, that both highly selective CCK1R and CCK2R agonists and antagonists have been described. In some cases the utility of the different compounds has been limited by their solubility, however both CCK1R agonists (GW 5823, SR146131, GI181771X) [45–47], CCK1R antagonists (loxiglumide, T-0632, L-364, 718)[48–50] and a number of members of different classes of CCK2R antagonists (dexloxiglumide, benzotriazepine analogue #49, CI-1015, YF 476, CI-988) [12,51–54] with high selectivity, that are orally active, have been described.

Use of CCK1R and CCK2R agonists and antagonists in humans (Tables 2)

In human studies both relatively nonselective CCK1R and CCK2R agonists (CCK) and antagonists (proglumide, loxiglumide, spiroglumide) as well as highly selective CCK1R and CCK2R agonists (CCK) and antagonists (Table 2) have been used to explore normal human physiology as well as various disease states [1•,2,3•,8•,14•,15•]. At present no CCK1R or CCK2R antagonist is approved in the United States (US) for diagnosis or treatment of any disorder. Both CCK1 and CCK2R agonists have been in clinical use for a number of years. Pentagastrin (Boc-βAla-CCK4) has long been used to measure maximal acid output in various clinical conditions. Because it was found to cause exaggerated stimulation of calcitonin release by interacting with CCK2Rs overexpressed on Medullary Thyroid Cancer (MTC) cells, it has been widely used in the past, prior to the availability of genetic tests, as a provocative test to identify patients with MTC, especially in families with the inherited autosomal dominant disorder, Multiple Endocrine Neoplasia type 2A,B [3•]. CCK (sincalide) has long been used to stimulate gallbladder emptying in studies of gallbladder function in various gallbladder and abdominal pain disorders such as acalculous cholecystitis [15•,55,56].

To understand the progress in the possible therapeutic use of these CCKR agonists or antagonists summarized in Tables 2 and 3 a few points on their use or results in human diseases will be briefly considered. The rationale for the use of CCK1R and CCK2R agonists or antagonists in various human disorders, especially those of the gastrointestinal tract, has been recently reviewed [3•,15•] and will be dealt with only briefly below. The results of recent studies of the use of CCKR agonists or antagonists, especially in non-gastrointestinal disorders (panic attacks, satiety, antitumor treatment and localization of tumors, nociception) will be briefly discussed. The use of these agents in various gastrointestinal disorders such as acute and chronic pancreatitis, motility disorders (functional dyspepsia, biliary colic, constipation, irritable bowel syndrome) and various hypergastrinemic states had been recently reviewed [3•,14•] and will not be dealt with in detail.

CCK1R/CCK2R agonists use in humans (nonapproved)

The principal area of therapeutic interest here is the possible use of CCK1R agonists for treatment of eating disorders/obesity [8]. Considerable laboratory data from animal studies on normal and genetic animal models as well as studies in humans provide strong support that CCK can function as a satiety factor [8•,57,58]. These studies show the satiety effect is primarily vagally mediated [8•,59,60]. These satiety effects in man are further supported by studies demonstrating that patients with the eating disorder, bulimia nervosa have impaired CCK secretion in response to a meal [61]. Recently the CCK1R agonist GI181771X was shown to be orally active in humans by inhibiting gastric emptying and to have an acceptable safety profile [47,62•]. The results were recently reported of a double blind 24-week randomized study examining the effect of GI181771X on body weight in 701 obese subjects [62•]. GI181771X did not reduce body weight, effect waist circumference or alter cardio-metabolic risk markers [62•]. GI181771X was well tolerated although there was an increased frequency of GI side effects in the drug treated group and two drug treated patients developed gallstone related pancreatitis [62•]. The exact reason that CCK1R monotherapy was ineffective remains unclear: possible explanations include the development of tachyphylaxis or other compensatory mechanisms that come into play long-term and are not seen in short-term studies [58,62•]. When CCK is given by continuous infusion intraperitoneally in rats the anorectic effect is also lost after 24 hours [41]. The authors concluded that CCK1R monotherapy is unlikely to have a role in human weight reduction [62•].

The CCK2R agonists, CCK-4 and pentagastrin are frequently used in humans to induce panic attacks to study novel agents in their treatment or for other study purposes [63–66].

CCK1R antagonists use in humans (nonapproved)

The primary areas of therapeutic interest with CCK1R antagonists include the various gastrointestinal disorders listed in a previous paragraph (Table 1). While the studies in GI diseases have not resulted in any licensed indication in the US for CCK1R antagonists, the CCK1R antagonist loxiglumide continues to be evaluated in Japan for possible efficacy in acute and chronic pancreatitis [48,67] and phase III studies with the CCK1R antagonist, dexloxiglumide, in constipation-dependent irritable bowel syndrome are planned in the US [14•,51].

CCK2R antagonists use in humans (nonapproved)

The primary areas of therapeutic interest with CCK2R antagonists include the various gastrointestinal disorders listed in a previous paragraph, potentiation of opioid analgesics, treatment of panic-anxiety disorders, CCK2R receptor directed imaging/radiotherapy of tumors and for possible antitumor treatment (Table 1).

Numerous animal and human studies demonstrate that activation of CCKRs results in an anti-opioid effect with involvement of both CCK1Rs and CCK2Rs and μ and δ opioid receptors [18,19,14•,69,70]. Selective CCK2R antagonists or antisense oligonucleotides potentiate the analgesic effect of morphine or endogenous enkephalins in rodents and numerous studies, including studies in CCK2R knockout mice, provide convincing evidence for a role of CCK2R in opioid analgesia and tolerance [19,70,71]. Studies in rats also suggest a role for CCK1R in opioid analgesia, because administration to rats of the selective CCK1R antagonist, L-364,718, enhances morphine analgesia and chronic treatment prevents the development of tolerance to morphine analgesia [17,19]. Numerous human studies with the nonselective CCKR antagonist, proglumide (Table 2), but not with the CCK2R antagonist, L-365, 260, demonstrated potentiation of opioid analgesia and/or prolonged duration of action [19,72]. Recently attempts have been made to synthesize peptide analogues that have agonist activity at μ and δ opioid receptors and function as a CCK2R antagonist [69]. Although progress has been made in

developing such compounds [69] none have been shown to be therapeutically useful in human studies. While the above results suggest CCK2R antagonists may be useful to enhance the analgesic effects of opioids in human, no large controlled studies have established their potential usefulness in man.

Panic disorder can be an incapacitating condition, current treatments are often inadequate and the life-long prevalence is 2.5–3% [24,25,64,65]. Animal studies using normals and CCK2R knockout animals as well as human studies, provide evidence that activation of CCK2R may play an important role in human panic disorders [1•,24,25,64]. In these studies CCK2R agonists (pentagastrin, CCK-4) [63–66] are able to induce panic disorders in humans and numerous short-term studies demonstrate various CCK2R antagonists can block their development [1•,24,25,64]. However, longer studies in humans using various CCK2 antagonists (CI-988, L-365,260) have not demonstrated efficacy in prevention of the panic disorders [73–75]. Whether this failure to see an effect is due to low drug bioavailability, to compensatory mechanisms or shows endogenous CCK2R agonists have no role in normal panic attacks, is at present unclear.

Many human tumors ectopically express or overexpress CCK2R and to a less extent CCK1R and gastrin-related peptides have tumor growth effects [15•,21,32•,34•,35]. This has led to two potential areas of therapeutic interest: the use of labeled CCK2R ligands to localize and possibly treat these tumors as well as the use of CCK2R antagonists to inhibit tumor growth [15•,21,32•,34•,35,36,76]. Each of these areas has been dealt with in the above references and only a few additional points related to their potential utility will be made here. No human studies have demonstrated the efficacy of CCK2R blockade for preventing tumor growth. Recently the results of two randomized controlled trials of gastrazole (JB5008) (Table 3) in advanced pancreatic cancer were reported [77••]. Trial A (18 patients) demonstrated an improved survival with gastrazole treatment ($p=0.02$), however Trial B (98 patients) demonstrated no improvement over 5-FU alone [77••]. In both trials gastrazole had low toxicity, which led the authors to suggest it should be tried in combination with other agents in the future [77••]. Numerous radiolabeled gastrin agonists have been described which can localize CCK2R expressing tumors in animal models and also localize tumor in patients with various neoplasms (medullary thyroid cancer, carcinoids, other neuroendocrine tumors), which overexpress CCK2R [36,76,78,79•]. In two recent studies [78,79•] involving patients with medullary thyroid cancer, carcinoids and other neuroendocrine tumors, gastrin receptor scintigraphy detected additional tumor locations to those detected by the widely used method of somatostatin receptor scintigraphy, suggesting it may play an important clinical role in the future. Whether it will also play a role for gastrin receptor mediated tumor cytotoxicity, similar to that shown with radiolabeled somatostatin analogues is at present unclear [36].

Conclusions

The lack of established therapeutic uses of CCK receptor ligands, especially the antagonists, is not now due to a lack of selective agonists or antagonists. As shown in Tables 2 and 3 there are a number of different classes of compounds, both orally active and parenterally active that have high selectivity for either CCK1R or CCK2R. These are starting to be used to explore the proposed role of these receptors in different pathophysiological conditions. In some cases, such as recently suggested from studies with CCK1R agonists in obesity or CCK2 antagonists in the prevention of panic disorders, these new studies show the animal paradigms are not adequately predictive of the human results and that monotherapy with these agents alone is not effective. However, in other cases both controlled human studies and additional animal studies need to be performed to clarify the possible therapeutic potential of these CCKR ligands. This is especially true for the possible use of CCK2R antagonists to potentiate the effect of analgesics or used in combination with other antitumor treatments, their use in hypergastrinemic states in

man especially induced by longterm PPI treatment [22], the utility of radiolabeled compounds to localize and treat tumors overexpressing CCK2R and the use of CCK1R antagonists for various GI disorders (pancreatitis, motility disorders). Lastly, it is important to realize that very few studies have been performed with these selective ligands examining the role of CCK1R and CCK2R in normal human physiology, especially in the CNS, with the result that it remains unclear which additional human disorders these could play a role in.

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Table 1

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

I. CCK1R Agonists/antagonists used in diseases**I. Agonists:**

- Obesity
- Gallbladder scintigraphy/assessment of function

II. Antagonists:

- a. Pancreatic disorder (acute/chronic pancreatitis)
- b. Gastrointestinal motility disorders (gallbladder disease, irritable bowel syndrome, functional dyspepsia, chronic constipation)
- c. Satiety disorders (anorexia nervosa, bulimia)
- d. Tumor growth

I. CCK2R agonist/antagonist used in diseases**I. Agonists:**

- a. Assessment of maximal acid output
- b. Detection of medullary thyroid cancer
- c. Induce panic attacks to assess various treatments.
- d. Imaging various tumors and delivering peptide receptor mediated radiotherapy

II. Antagonists:

- a. Hypergastrinemic states [physiological (atrophic gastritis, pernicious anemia), and pathological (Zollinger-Ellison syndrome)]
- b. Abnormalities due to gastric mucosal effects of hypergastrinemia (ECL cell hyperplasia, carcinoids, ↑ parietal cell mass)
- c. Acid-peptic disorders
- d. Panic disorders
- e. Potentiation of analgesics
- f. Tumor growth

Data are from [1•,3•,8•,14•,15•,21,35,48]

Table 2CCK1R and CCK2R agonists and antagonist used in human studies^(a)

	K _i or IC ₅₀ (μM)		Fold CCK1R preferring
	CCK1R	CCK2R	
<hr/>			
<i>CCK1R preferring</i>			
I. AGONISTS			
<i>A. Peptides</i>			
CCK-8	0.0028	0.0057	2
<i>B. 1, 5 benzodiazepine analogues</i>			
GI18177X [62]	NR	Antag	NR
<i>C. Thiazole derivative</i>			
SR 14613 ^b	0.0004	0.23	580
II. ANTAGONISTS			
<i>A. Glutaramic acid analogues</i>			
Proglumide ^c	6,000	11,000	1.8
Lorglumide (CR 1409) ^d	0.13	300	2,300
Loxiglumide (CR 1505) ^e	0.33	9.9	30
Dexloxiglumide (CR 2017) ^f	0.12	22	170
<i>B. 1,4 Benzodiazepines</i>			
L-364,718 (MK-329, Devazepide) ^g	0.00008	0.27	3,400
<i>C. Other</i>			
Linript (SI-27897) ^h	0.00058	0.49	843
			Fold CCK2R preferring
<hr/>			
<i>CCK2R preferring</i>			
I. AGONISTS			
<i>A. Peptides</i>			
Pentagastrin	2.8	0.0029	968
CCK-4	18.6	0.11	166
II. ANTAGONISTS			
<i>A. Glutaramic acid analogues</i>			
Spiroglumide (CR 2194) ⁱ	13.5	1.4	9.6
Itriglumide (CR 2945) ^j	20.7	0.0023	9,000
<i>B. 1,4 Benzodiazepines</i>			
L-365,360 ^k	0.28	0.002	140
YF476 ^l	0.50	0.00011	5,020
<i>C. Dipeptoids</i>			
CI-988 (PD-134,308) ^m	4.3	0.0017	2,501
<i>D. Benzobicyclo[2.2.2]octane</i>			
JB95008 (Gastrazole)	4.0	0.001	4,000

^aData from [1••,3••,46,62••,80,81]^b(2-[4-(4-chloro-2,5-dimethoxyphenyl)-5-(2-cyclohexyl-ethyl)-thiazol-2-ylcarbamoyl]-5,7-dimethyl-indol-1-yl)-1-acetic acid)^cD, L-4-benzamido-N,N-dipropyl-glutarmic acid]^d[D, L-4-(3,4-dichlorobenzoylamino)-5-(di-N-pentylamino)-5-oxopentanoic oxid]^e[D, L-4-(3,4 dichlorobenzamido)-N-(3-methoxypropyl)-N-pentylglutaramic acid]^f[(R)-4-(3,4-dichlorobenzoylamino)-5-[N-(3-methoxypropyl)-N-pentylamino]-5-oxopentanoic acid]^g[3S(-)-N(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepine-3-yl)-1H-indole-2-carboxamide]^h1-[(2-(4-(2-chlorophenyl)thiazole-2-yl)aminocarbonyl]indolyl) acetic acidⁱ(R)-8-Azaspino[4,5]decaane-8-pentanoic acid^j(R)-1-naphtalene propionic acid^k3-R(+)-(N-2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1 H-1,4 benzodiazepin-3-yl)-N'-(3-methylphenyl)urea^l((R)-1-[2.3 dihydro-2-oxo-1-pivaloylmethyl-5-(2'pyridyl)-1H-1,4-benzodiazepin-3-yl]-3-(methylamino-phenyl)urea^m4-[[2-[[3-(1H-indol-3-yl)-2-methyl-1-oxo-2[[[(tricyclo[3.3.1]dec-2-ylloxy)-carbonyl]amino]-propyl]amino]-1-phenylethyl]amino]-4-oxo-[R-(R*,R*)]-butanoate N-methyl-D-glucamine

Table 3
Highly subtype-selective CCK1R and CCK2R agonists and antagonists not used in human studies^a

	K _i or IC ₅₀ (μM)		
	CCK1R	CCK2R	Fold CCK1R preferring
<hr/>			
<i>CCK1R preferring</i>			
I. AGONISTS			
<i>A. Peptides</i>			
A-71378	0.0005	0.57	1140
A-71623	0.0037	4.4	1200
AR-15849	0.00003	0.198	6600
<i>B. 1,5 Benzodiazepines</i>			
GW 5823	0.023	1	45
II. ANTAGONISTS			
<i>A. Glutaramic acid analogues</i>			
A-65186	0.005	3.5	690
JNJ-17156516	0.011	1.7	150
<i>B. 1,4 Benzodiazepines</i>			
FK-480 (pranazepide)	0.0006	310	500
<i>C. 1,3-Dioxoperhydropyrido [1,2-C]pyrimidine analogues</i>			
IQM-95,333	0.00062	>5	>8,000
<i>D. Pyrazolidinone and related heterocyclic analogues</i>			
SC-50,998	0.0016	>10	>625
<i>E. Indol-2-one analogues</i>			
T-0632	0.00024	5.6	23,000
<i>E. Other analogues</i>	0.0012	1.8	1,500
TP-680			
			Fold CCK2R preferring
<hr/>			
<i>CCK2R preferring</i>			
I. AGONISTS			
<i>A. Peptides</i>			
BC-254	2.5	0.0006	4,200
JMV-310	13	0.0013	10,000
A-63387	6.3	0.0007	9,000
RB400	>3	0.00042	>7,200
SNF 9007	>1.2	0.00079	>1518
II. ANTAGONISTS			
<i>A. Glutaramic acid analogues</i>			
CR 2622	13.5	0.020	370
<i>B. 1,4 Benzodiazepines</i>			
L-368,935	1.4	0.00014	10,000
L-708,474	1.8	0.3	6,000
L-736,380	0.4	0.00005	8,000
L-740,093	1.6	0.0001	16,000
YM022	0.063	0.00007	930
<i>C. Dipeptoid analogues</i>			
CI-105	2.9	0.00014	10,000
<i>D. 1,5 Benzodiazepines</i>			
GV191869X	2.0	0.003	970
<i>E. 1-Benzazepine-2-one analogues</i>			
CP310,713	1.4	0.0001	14,000
<i>F. Benzotriazepine analogues</i>			
JB99157 [12,80]	0.019	10	>500
Cmp #49 [12]	0.00011	0.47	4270
<i>G. Ureidoacetamide analogues</i>			
RP69758	4.7	0.0043	1,200
RP72540	2.8	0.0012	2,300
D51-9927	0.17	0.00006	2,800
RP73870	1.6	0.00048	3,400
<i>H. Quinazoline-based analogues</i>			
LY-202769	>10	0.009	>1,100
<i>I. Benzobicyclo[2.2.2]octane</i>			
JB93182	2.8	0.0011	3,300
<i>J. Pyrazolidinone and related heterocyclic analogues</i>			
LY288513	20.5	0.019	1,100
<i>K. Indol-2-one analogue</i>			
AG-041R	0.55	0.0011	500
<i>L. Other analogues</i>			
Tetronothiodin	>10	0.0036	>27,000

^a Data and structures from [2,3•,4,6•,8•,9,62•,80,82]