

# Cholecystokinin and Gastrin Receptors

## Key References

- Chambers, M.S., Fletcher, S.R. "CCK-B antagonists in the control of anxiety and gastric acid secretion." *Prog. Med. Chem.* **37**, 45-81 (2000).
- deTullio, P. et al. "Recent advances in the chemistry of cholecystokinin receptor ligands (agonists and antagonists)." *Curr. Med. Chem.* **6**, 433-455 (1999).
- Dockray, G.J. "Topical review. Gastrin and gastric epithelial physiology." *J. Physiol.* **518**, 315-324 (1999).
- Dunlop, J. "CCK receptor antagonists." *Gen. Pharmacol.* **31**, 519-524 (1998).
- Fink, H. et al. "Major biological actions of CCK - a critical evaluation of research findings." *Exp. Brain Res.* **123**, 77-83 (1998).
- Henke, B.R. et al. "Optimization of 3-(1H-indazol-3-ylmethyl)-1,5-benzodiazepines as potent, orally active CCK-A agonists." *J. Med. Chem.* **40**, 2706-2725 (1997).
- Jensen, R.T. "CCK<sub>B</sub>-gastrin receptor antagonists. Recent advances and potential uses in gastric secretory disorders." *Yale J. Biol. Med.* **69**, 245-259 (1996).
- Koh, T.J., Chen, D. "Gastrin as a growth factor in the gastrointestinal tract." *Regul. Pept.* **25**, 37-44 (2000).
- Noble, F., Roques, B.P. "CCK-B receptor: Chemistry, molecular biology, biochemistry and pharmacology." *Prog. Neurobiol.* **58**, 349-379 (1999).
- Noble, F. et al. "International Union of Pharmacology, XXI, structure, distribution and functions of cholecystokinin receptors." *Pharmacol. Rev.* **51**, 745-781 (2000).
- Rehfeld, J.F. "The cholecystokinin-gastrin family of peptides and their receptors." *Results Probl. Cell Differ.* **26**, 293-321 (1999).
- Ritter, R.C. et al. "Cholecystokinin: Proofs and prospects for involvement in control of food intake and body weight." *Neuropeptides* **33**, 387-399 (1999).

## Overview

The naturally occurring peptides, cholecystokinin (CCK) and gastrin closely resemble each other at their carboxyl terminus, which is the biologically active portion of the molecules. Both peptides contain the C-terminal sequence Gly-Trp-Met-Asp-Phe-NH<sub>2</sub>; however, they differ in the presence or absence of a sulfated tyrosine in position 7 from the carboxyl terminal amide. CCK immunoreactivity is widely distributed in the CNS and gastrointestinal tract, whereas gastrin immunoreactivity is more localized, occurring predominantly in gastric antral and duodenal G cells, with low levels in various neuroendocrine tissues (pituitary, adrenal medulla, vagus), genital and respiratory tracts. Some normal and malignant tissues synthesize immature forms of gastrin (particularly glycine-extended forms) with minimal fully processed amidated forms.

CCK is thought to function primarily as a neurotransmitter/hormone/neuromodulator, whereas gastrin functions primarily as a hormone. CCK exerts effects on numerous tissues, including the CNS where it modulates dopaminergic activity and opioid analgesia. In the periphery, it modulates cell growth (pancreas and various tumors), stimulates pancreatic exocrine secretion and insulin release, modulates gut motility (contraction of the gall bladder, intestinal smooth muscle, delayed gastric and colonic motility), alters gastric secretion (release of pepsinogen, somatostatin, inhibition of acid secretion) and stimulates peripheral neural pathways involved in gut motility, satiety and pancreatic secretion.

Gastrin has stimulatory effects on gastric acid secretion, trophic effects on the gastric mucosa, stimulatory effects on

growth of numerous tumors and produces anxiogenic effects in the CNS. There is also experimental evidence to suggest that gastrin or its precursor forms may have a growth effect in colon cancer, although this remains controversial.

Two receptors mediate the effects of these peptides; a CCK<sub>A</sub> receptor and a CCK<sub>B</sub> receptor (also previously called a gastrin receptor). The structures of both receptors are known and reveal that both are members of the seven transmembrane spanning superfamily of G protein-coupled receptors. In humans, the 428 amino acid CCK<sub>A</sub> receptor and the 447 amino acid CCK<sub>B</sub> receptor have 48% homology. However, they differ in their distribution, their affinities for the natural agonists CCK and gastrin, and their affinities for a number of synthetic agonists and antagonists. The CCK<sub>B</sub> receptor is the predominant subtype in the CNS where it is widely distributed, however, it also occurs in abundance in the gastrointestinal tract. The CCK<sub>A</sub> receptor has a more limited distribution with highest densities in the hypothalamic nuclei, areas of the hippocampus, the septum, dorsal motor vagal nucleus and interpeduncular nucleus of the brain stem. It also occurs in numerous gastro-intestinal tissues. The naturally occurring sulfated CCK analogs possess high affinity for both the CCK<sub>A</sub> receptor and the CCK<sub>B</sub> receptor and are thus non-discriminatory. Gastrin and desulfated forms of CCK display a high affinity for the CCK<sub>B</sub> receptor, but not the CCK<sub>A</sub> receptor. It has been proposed that a distinct, specific CCK/gastrin receptor mediates growth effects of glycine-extended gastrins, although this remains unproven and controversial.

Activation of both receptors is coupled to stimulation of phospholipase C, leading to the generation of inositol phosphates, mobilization of cellular calcium and activation of protein kinase C. Recent studies show that activation of both receptors also causes tyrosine phosphorylation of a number of proteins, including p125 focal adhesion kinase (FAK) and paxillin, in addition to activating the MAP kinase cascade.

The important effects of these peptides that have been the focus of much attention from the drug industry include: for the CCK<sub>A</sub> receptor - satiety, potentiation of opiate analgesia, gut motility effects and growth-promoting effects on some tumors, and for the CCK<sub>B</sub> receptor - anxiogenic effects, growth effects on the gastric mucosa, gastric enterochromaffin-like (ECL) cells and numerous tumors and effects on acid secretion. The possible role of aberrantly expressed gastrin precursors by colon cancer is also an important area of current investigation.

# Cholecystokinin and Gastrin Receptors

<b>CURRENTLY ACCEPTED NAME</b>	CCK <sub>A</sub> ( <a href="#">C 6980</a> )	CCK <sub>B</sub>
<b>ALTERNATE NAME</b>	CCK <sub>1</sub>	CCK <sub>2</sub> , gastrin
<b>STRUCTURAL INFORMATION</b>	428 aa (human)	447 aa (human)
<b>SUBTYPE SELECTIVE AGONISTS</b>	A 71378 A 71623 AR-R 15849 GW 5823	BC-264 Gastrin I ( <a href="#">G 9020 (h)</a> , <a href="#">G 1276 (r)</a> ) and Gastrin II ( <a href="#">G 1260</a> ) CCK-8 desulfated ( <a href="#">C 2901</a> )
<b>SUBTYPE SELECTIVE ANTAGONISTS</b>	L-364,718 (Devazepide) Lorglumide ( <a href="#">L-109</a> ) PD 140,548 TP-680 T-0632 SR 27897	YM022 L-740,093 L-365,260 L-156,586 LY-262691 Ureidoacetamides (RP 69758, RP 72540, RP 73870) Tetronothiodin Peptoid analogs (CI-988, CI-1015) YF476 GV150013
<b>RECEPTOR SELECTIVE AGONIST</b>	CCK-8 ( <a href="#">C 2175</a> )	CCK-8 ( <a href="#">C 2175</a> )
<b>RECEPTOR SELECTIVE ANTAGONISTS</b>	Benzotript Proglumide ( <a href="#">M-006</a> )	Benzotript Proglumide ( <a href="#">M-006</a> )
<b>SIGNAL TRANSDUCTION MECHANISMS</b>	G <sub>q/11</sub> (increase IP <sub>3</sub> /DAG)	G <sub>q/11</sub> (increase IP <sub>3</sub> /DAG)
<b>RADIOLIGANDS OF CHOICE</b>	[ <sup>125</sup> I]-BH-CCK-8 [ <sup>3</sup> H]-L-364,718	[ <sup>125</sup> I]-BH-CCK-8 [ <sup>3</sup> H]-L-365,260 [ <sup>125</sup> I]-Gastrin [ <sup>3</sup> H]-propionyl-BC-264 [ <sup>3</sup> H]-PD 140,376 [ <sup>3</sup> H]-PD 142,308

## ABBREVIATIONS

**A 71378:** [Desamino,Nle<sup>28,31</sup>,N-methyl-Asp<sup>32</sup>] CCK-27-33

**A 71623:** Boc-Trp-Lys(ε-N-2-Methycarboxybenzoyl)-Asp-Phe-NH<sub>2</sub>

**AR-R 15849:** Hpa(SO<sub>3</sub>H)-Nle-Gly-Trp-Nle-MeAsp-Phe-NH<sub>2</sub> where, Hpa(SO<sub>3</sub>H)=sulfated 4-hydroxyphenylacetyl

**BC-264:** Boc-Tyr(SO<sub>3</sub>H)-gNle-mGly-Trp-(NMe)Nle-Asp-Phe-NH<sub>2</sub>

**CI-988:** 4-[[2-[[3-(1H-indol-3-yl)-2-Methyl-1-oxo-2[[[tricyclo[3.3.1.1<sup>2,7</sup>]dec-2-yloxy]-carbonyl]amino]-propyl]amino]-1-phenylethyl]amino]-4-oxo-[R-(R\*,R\*)]-butanoate N-methyl-D-glucamine

**CI-1015:** tricyclo[3.3.1.1<sup>3,7</sup>]dec-2-yl [1S-[1α(S\*)2β]-[2-Hydroxycyclohexyl]amino]-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxoethyl]carbamate

**GV150013:** (+)-N-(1-[1-adamantane-1-methyl]-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-3-yl)-N'-phenylurea

**GW 5823:** 2-[3-(1H-indazol-3-ylmethyl)-2,4,dioxo-5-phenyl-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]-N-isopropyl-N-(methoxyphenyl)acetamide

**L-156,586:** 15-Dihydro-13,14-anhydro-virginamycin M1

**L-364,718:** [3S(-)-N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepine-3-yl)-1H-indole-2-carboxamide] and lorglumide [D,L-4-(3,4-dichlorobenzoylamino)-5-(N-3-methoxypropyl-pentylamino)-5-oxopentanoic acid]

**L-365,360:** 3-R(+)-(N-2, 3-Dihydro-1-methyl-2-oxo-5-phenyl-1 H-1, 4-benzodiazepin-3-yl)-N'-(3-methylphenyl)urea

**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)

**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

**LY-262691:** 1-(4-Bromophenylaminocarbonyl)-4, 5-diphenyl-3-pyrazolidinone

**PD 140,376:** L-3-[[4-Aminophenyl]methyl-N-[[tricyclo(3.3.1.1<sup>3,7</sup>)dec-2-yloxy]carbonyl]-D-tryptophyl]-β-alanine

**PD 140,548:** N-(α-Methyl-N-[[tricyclo(3.3.1.1<sup>3,7</sup>)dec-2-yloxy]carbonyl]-L-tryptophyl)-D-3-(phenylmethyl)-β-alanine

**PD 142,308:** iodinated PD 140548

**RP 69758:** (3-[3-[N-(N-Methyl N-phenyl-carbamoylmethyl)N-phenyl-carbamoylmethyl]ureido]phenyl)acetic acid

**RP 72540:** ((RS)-{3-[3-[N-(3-Methoxy phenyl) N-(N-methyl N-phenyl-carbamoylmethyl)carbamoylmethyl]ureido]phenyl}propionic acid

**RP 73870:** (RS)-{[[N-(Methoxy-3-phenyl)-N-(N-methyl-N-phenyl-carbamoylmethyl)-carbamoyl-methyl]-3-ureido]-3-phenyl]-2-ethylsulfonate

**SR 27897:** 1-[(2-(4-(2-Chlorophenyl)thiazole-2-yl)aminocarbonyl]indolyl]acetic acid

**T-0632:** [sodium (S)-3-[1-(2-Fluorophenyl)-2,3-dihydro-3-[(3-isoquinolyl)-carbonyl]amino-6-methoxy-2-oxo-1H-indole]propanoate]

**TP-680:** (R)-1-[3-(3-Carboxypyridine-2-yl)-thio-2-(indol-2-yl)carbonylamino]propionyl-4-diphenylmethylpiperazine

**YF476:** ((R)-1-[2,3-Dihydro-2-oxo-1-pivaloylmethyl-5-(2'-pyridyl)-1H-1,4-benzodiazepin-3-yl]-3-(3-methylamino-phenyl)urea)

**YM022:** ((R)-1-[2, 3-Dihydro-1-(2'-methylphenacyl)-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl]-3-(methylphenyl)urea

**h:** human  
**r:** rat

## FOOTNOTES