

Cholecystokinin and Gastrin Receptors

Key References

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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-NH₂; however, they differ in the presence or absence of a sulfated tyrosine in position 7 (CCK) or 6 (gastrin) 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 pro-gastrin and 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 experimen-

tal 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_A (or CCK-1) receptor and a CCK_B (or CCK-2) 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_A receptor and the 447 amino acid CCK_B 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_B receptor is the predominant subtype in the CNS where it is widely distributed, however, it also occurs in abundance in the gastro-intestinal tract. The CCK_A 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_A receptor and the CCK_B receptor and are thus non-discriminatory. Gastrin and desulfated forms of CCK display a high affinity for the CCK_B receptor, but not the CCK_A receptor. It has been proposed that a distinct, specific CCK/gastrin receptor mediates growth effects of progastrin and 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 activa-

tion 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_A receptor - satiety, pancreatitis, gut motility effects and growth-promoting effects on some tumors, and for the CCK_B receptor - anxiogenic effects, anti-opioid 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.

Cholecystikin and Gastrin Receptors

CURRENTLY ACCEPTED NAME	CCK _A (C6980)	CCK _B
ALTERNATE NAME	CCK1	CCK2, gastrin
STRUCTURAL INFORMATION	428 aa (human)	447 aa (human)
SUBTYPE SELECTIVE AGONISTS	A 71378, A 71623, AR-R 15849, GW 5823	BC-264 Gastrin I (G9020 (h), G1276 (r)) and Gastrin II (G1260), CCK-8 desulfated (C2901)
SUBTYPE SELECTIVE ANTAGONISTS	L-364,718 (Devazepide), Lorglumide (L109), PD 140,548, T-0632, TP-680, 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
RECEPTOR SELECTIVE AGONIST	CCK-8 (C2175)	CCK-8 (C2175)
RECEPTOR SELECTIVE ANTAGONISTS	Benzotript, Proglumide (M006)	Benzotript, Proglumide (M006)
SIGNAL TRANSDUCTION MECHANISMS	G _{q/11} (increase IP ₃ /DAG)	G _{q/11} (increase IP ₃ /DAG)
RADIOLIGANDS OF CHOICE	[¹²⁵ I]-BH-CCK-8, [³ H]-L-364,718	[¹²⁵ I]-BH-CCK-8, [³ H]-L-365,260, [¹²⁵ I]-Gastrin, [³ H]-propionyl-BC-264, [³ H]-PD 140,376, [³ H]-PD 142,308
TISSUE EXPRESSION	CNS [limited brain area (n. tractus solitarius, area postrema, n. interpuncularis, posteromedial part of n. accumbens)], GI tract (gallbladder, pylorus, intestine, vagus, spinal cord, islets)	CNS [widely in brain (highest cerebral cortex, n. caudatus, anterolateral part of n. accumbens)], GI tract (stomach, vagus), CNS (regulation of the opioid system, stress-anxiety)
PHYSIOLOGICAL FUNCTION	Inhibits feeding, potentiates dopamine behavior, GI tract (gallbladder contraction, pancreatic enzyme and fluid secretion, inhibits gastric emptying, LES tone, colonic transit, Inhibition acid secretion;	GI tract (stimulates acid secretion), growth gastric enterochromaffin-like cells
DISEASE RELEVANCE	Satiety, eating disorders (bulimia), pancreatitis, chronic constipation of aged, gallbladder disease, functional dyspepsia and irritable bowel syndrome	Acid secretory disorders (<i>H. pylori</i> infection, Zollinger-Ellison syndrome), development of gastric carcinoids in hypergastrinemic states, potentiate opioid analgesia, anxiety and panic disorders, tumorigenesis/growth (colon, pancreatic, gastric)

Cholecystinin and Gastrin Receptors

Abbreviations

A 71378: [Desamino,Nle^{28,31},N-methyl-Asp³²] CCK-27-33
A 71623: Boc-Trp-Lys(e-N-2-Methcarbonyl)-Asp-Phe-NH₂
AR-R 15849: Hpa(SO^{3H})-Nle-Gly-Trp-Nle-MeAsp-Phe-NH₂ where, Hpa(SO_{3H})=sulfated 4-hydroxyphenylacetyl
BC-264: Boc-Tyr(SO^{3H})-gNle-mGly-Trp-(NMe)Nle-Asp-Phe-NH₂
CI-988: 4-[[[3-(1H-indol-3-yl)-2-Methyl-1-oxo-2[[tricyclo[3.3.1.1,7]dec-2-yloxy]-carbonyl]amino]-propyl]amino]-1-phenylethyl]amino]-4-oxo-[R-(R*,R*)]-butanoate N-methyl-D-glucamine
CI-1015: Tricyclo[3.3.1.1,13,7]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 loxiglumide [D,L-4-(3,4-dichloro-benzoylamino)-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-[[3(R)-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(3.3.1.1,13,7)dec-2-yloxy)carbonyl]-D-tryptophyl]-β-alanine
PD 140,548: N-(α-Methyl-N-[(tricyclo(3.3.1.1,13,7)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-Methoxyl 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-isoquinoliny)-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

FOOTNOTES

h: human
r: rat