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Cholecystokinin Type 1 Receptor

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Gene Symbol: CCKAR

1. General aspects of CCK receptor structure and function

Cholecystokinin (CCK) exerts its physiological actions through the activation of two structurally-related class A G protein-coupled receptors (GPCRs) identified as type 1 CCK receptor (CCK1R) and type 2 CCK receptor (CCK2R) (also known as CCKAR and CCKBR, respectively, related to their prominent presence in “alimentary tract” and “brain”) (14, 47). These receptors have an extracellular amino-terminal tail domain, seven hydrophobic segments representing transmembrane helices that are connected by intracellular and extracellular loops to form a helical bundle domain, and an intracellular carboxyl-terminal tail. These receptors are highly homologous to each other and share 50% overall identity, with the transmembrane segment regions reaching 70% identity (47). The focus of this article is on the type 1 receptor, CCK1R. CCK peptides of different lengths with a common carboxyl-terminal-amide sequence are produced from a single 115-residue preprohormone precursor. Mature peptides range from 58, 39, 33, to 8 residues, with each containing a sulfated tyrosine residue seven residues from the carboxyl terminus (15, 47, 62). The CCK1R requires the carboxyl-terminal CCK heptapeptide-amide that includes a sulfated tyrosine for high affinity binding and full biological potency (47). This is in contrast to the CCK2R that only requires the carboxyl-terminal tetrapeptide-amide that is shared by CCK and gastrin, and that is not influenced by the sulfation state of the tyrosine residue.

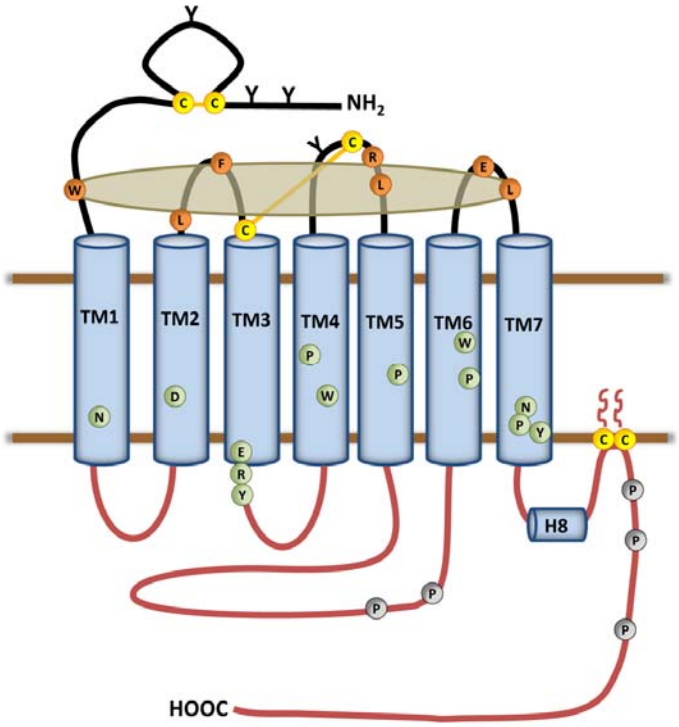

Figure 1. Shown is a two-dimensional representation of the sequence of the class A GPCR, CCK1R, highlighting some typical features of this receptor. It has typical heptahelical topology, with the amino-terminal tail outside the cell and the carboxyl-terminal tail inside the cell. Sites of glycosylation (Y) exist on ectodomains, while sites of phosphorylation are present intracellularly (grey 'P' circles). There are two disulfide bonds (connecting the cysteines) within the amino-terminal tail and linking the top of TM3 with ECL2. There is a site of palmitoylation within the carboxyl-terminal tail (two Cs anchored), helping to establish helix 8 adjacent to the inside of the plasma membrane. Also shown are typical signature sequences of the class A GPCR family (residues represented in green circles). Also illustrated is a proposed docking model for the natural CCK peptide (oval) at the CCK1R, noting key receptor residues thought to be at the interface with this ligand.

The CCK1R belongs to the class A group of GPCRs (47) having signature sequences typical of this family (Fig 1). This includes E/DRY at the intracellular side of transmembrane segment three and NPxxY at the intracellular side of transmembrane segment seven. The cDNA encoding the CCK1R was first cloned from the rat pancreas by Wank *et al*. (80), and subsequently from the human gallbladder (77), with the chromosomal localization of this human receptor gene identified soon thereafter (9). The mature receptor is glycosylated and has a conserved disulfide bond between predicted extracellular loops one and two, and an additional intradomain disulfide bond within its amino terminus in the human receptor. This receptor is phosphorylated on serine and threonine residues in intracellular loop three and in the carboxyl-terminal tail in response to agonist stimulation. Relevant kinases that phosphorylate this receptor include protein kinase C and a staurosporine-insensitive G protein-coupled receptor kinase (19). A prominent function of receptor phosphorylation is to interfere with receptor coupling to G proteins, thereby desensitizating the signaling system (61). This receptor also has two cysteine residues representing sites of palmitoylation intracellularly beneath the predicted seventh transmembrane segment, which help to attach an eighth helical segment to the cytosolic face of the bilayer. The carboxyl-terminal tail has been shown to contribute determinants for ligand-induced internalization of the CCK1R (3), although phosphorylation of this region was found to not be required (61).

Agonist stimulation of CCK1R induces a conformational change in the receptor that results in receptor coupling with Gq, which leads to subsequent PLC activation and an increase in intracellular calcium levels from IP_3-sensitive stores. Extensive studies have shown that the agonist-occupied Gq-coupled receptor state represents a high affinity state of this receptor (46, 87, 89). The CCK1R has also been shown to be capable of coupling with Gs upon stimulation by high concentrations of CCK, thereby also resulting in increases in cAMP (70, 84, 85, 90). Mutation of Asn^{82} in the first intracellular loop has been shown to disrupt this action (84). CCK1R has also been also shown to couple with G_{13} that results in activation of a RhoA pathway (44).

A broad range of experimental approaches have been utilized to study the molecular basis of CCK binding to the CCK1R (refer to review (47) for details). While there has been some controversy regarding the interpretation of these studies, the most consistent pose of the bound peptide is along the extracellular surface of the membrane, with its carboxyl-terminal phenylalanine-amide adjacent to the area above transmembrane segment one (27, 49). A contrasting model has been proposed based largely on mutagenesis data in which the carboxyl terminus of the peptide dips into the bilayer within the helical bundle (29), however this interpretation is not compatible with several observations. Most recently, it has been shown that benzodiazepine ligands that occupy the intramembranous pocket proposed to be the location of the carboxyl terminus of CCK in this model are clearly allosteric ligands, able to bind in location that is distinct to that occupied by bound CCK (1, 4, 7, 18). Mutagenesis approaches including segmental deletions and site-specific modifications, as well as chimeric receptor constructs for CCK1R, have been used to provide indirect insights into residues that contribute to ligand binding and signaling (42, 49, 69). Photoaffinity labeling is another approach that has been used, where modified high affinity, biologically active CCK probes with sites of covalent attachment throughout the CCK pharmacophore have provided direct evidence for the spatial approximation between residues within the bound CCK ligand and CCK1R (11-13). Here, too, the carboxyl-terminal residue of CCK was directly shown to be spatially approximated with a residue in the receptor amino terminus, above the top of transmembrane segment one. Additionally, fluorescence-based techniques exploring the microenvironment of receptor-docked CCK fluorescent analogues have also been used. Here a fluorescence indicator was incorporated at different positions of the CCK pharmacophore, and properties such as anisotropy, fluorescence lifetime, iodide quenching, and red-edge excitation shifts for each probe were determined, providing additional insights into the molecular basis of CCK binding to CCK1R (24-27) (refer to (10) for summary of behavior of various fluorescent probes).

Different non-natural ligands displaying high selectivity for the CCK receptor and potency have been developed (see reviews (30, 33)). A group of benzodiazepine compounds has been most extensively studied in regard to mechanism of binding to CCK1R (1, 4, 7, 18, 23). Studies incorporating receptor mutagenesis, photoaffinity labeling, and pharmacological manipulations have clearly shown that these ligands bind to a distinct allosteric site within the intramembranous helical bundle that is distinct from the orthosteric CCK peptide-binding site of CCK1R (4, 18, 22, 40). It has been shown that for the binding of the CCK1R-selective benzodiazepine-based antagonist, transmembrane segments six and seven (residues 6.51, 6.52, and 7.39 (2)*****) are most critical (4). Also, recently an optimal model showing the binding of a benzodiazepine-based CCK1R agonist has been reported that demonstrates a distinct conformation of this binding pocket within the transmembrane helical bundle from that which accommodates the structurally-related antagonist. This study revealed a key role for Leu(7.39) that was

predicted to interact with the isopropyl group in the N1 position of the benzodiazepine that acts as a "trigger" for biological activity, whereas the role of this residue is currently less clear for chemically distinct agonists (23).

CCK1R is also sensitive to the cholesterol composition of the membrane, in contrast to CCK2R that is not sensitive to this lipid. Membrane cholesterol depletion has been shown to reduce CCK binding affinity to CCK1R, as well as to decrease the biological response to this hormone at that receptor. Increased membrane cholesterol has been shown to be associated with an increase in CCK binding affinity; however, the biological responses to CCK under these conditions have been shown to be lower than normal as well. Some structural determinants for cholesterol sensitivity have been reported to be present within the third exon of CCK1R, which encodes most of transmembrane segment three and segment four, including one CRAC (cholesterol recognition/interaction amino acid consensus) motif and one CCM (cholesterol consensus) motif (10, 20, 21, 28, 59).

CCK elicits a variety of physiological responses via the CCK1R, including a broad variety of important functions, such as stimulation of gallbladder contraction, stimulation of pancreatic exocrine secretion, relaxation of the sphincter of Oddi, inhibition of gastric acid secretion, delay of gastric emptying, and induction of post-cibal satiety (38, 68). The CCK1R is present in various parts of the gastrointestinal tract, such as gallbladder muscularis, neurons controlling pancreatic secretion, D cells in the gastric mucosa (68), muscularis propria of gastric antrum, fundus and pylorus (63), and vagal afferent neurons (refer to review (14) for details).

The CCK1R gene is located on human chromosome 4p15.1-p15.2 and on mouse chromosome 5 (31, 65). Factors regulating levels of expression of this gene have not been extensively studied.

CCK seems to be involved in pathologic states, such as irritable bowel syndrome, where CCK1R antagonists have been studied as potential treatments (67, 78). It has also been utilized extensively in experimental models of pancreatitis, where CCK hyperstimulation can cause this disorder (64). However, CCK1R antagonists have not been useful in the management of clinical pancreatitis. Reduced responsiveness of the CCK1R has also been shown to contribute to the pathogenesis of gallbladder diseases. Reduced gallbladder muscle contraction in response to CCK has been demonstrated in patients with cholesterol gallstones, as opposed to those with pigment gallstones. This defect in receptor function seems to be caused by the effect of increased membrane cholesterol in this condition (5, 6, 86, 88). A role of CCK1R in development of obesity has been proposed because of its importance in inducing satiety responses (41, 54). Polymorphisms of the CCK1R have also been associated with increased body fat content in some patients (16, 39, 72), however further studies will be necessary to validate a role for these polymorphisms in obesity. Polymorphisms in the CCK1R gene have also been described in some patients with panic disorder, Parkinson’s disease, and alcohol dependence, however this receptor is not believed to play a quantitatively important role in these problems (51, 52, 79). A rare clinical syndrome has been reported in which there is an abnormal trans-acting splicing factor that results in most of the CCK1R being misprocessed, with the third exon spliced out, and thereby yielding a non-functional receptor. This caused a profound reduction in expression levels of the receptor and was associated with obesity and premature gallstones (48). CCK1R is shown to be present in certain types of cancers; although its role remains unclear. Immunohistochemical analyses have shown the presence of CCK1R in ductular adenocarcinoma cells from some pancreatic tumors (82). CCK1R has also been shown to be

* According to the Ballesteros and Weinstein GPCR numbering system (2) , amino acid residues predicted to reside within a transmembrane (TM) segment are assigned two numbers (N1,N2), where N1 represents the TM segment number and N2 represents sequential numbering relative to the most conserved residue in and the segment that is assigned 50.

heterogeneously expressed in some ileal carcinoids (75).

2. Specific aspects of CCK receptor function in the pancreas

The most widely recognized physiological role of CCK is stimulation of pancreatic enzyme secretion. It has become clear, however, that the cellular basis for this may vary among species. The early and clearly definitive studies focused on the rodent pancreatic acinar cell. There is convincing evidence for the expression of functional CCK1R on rodent acinar cells, as demonstrated by receptor mRNA expression, CCK ligand binding assays, and *in vitro and in vivo* functional secretory responses to physiological concentrations of CCK (66, 83).

However, until recently, the expression and cellular distribution of CCK1R in human pancreas was less clear, and has been a subject of considerable debate. This is mainly due to the very low levels of expression of CCK1R mRNA in human pancreas compared with rodent pancreas (32, 81). Immunohistochemical studies have also failed to localize CCK1R to the human pancreas. An early report utilizing reverse-transcriptase PCR showed very low levels of expression of CCK1R mRNA in adult human pancreas, although Northern blotting approaches failed to detect the expression. The same study also reported the expression of CCK1R mRNA in human fetal (mid-trimester) and infant (50 days old) pancreas (57). A more recent study utilizing a quantitative PCR technique on several samples from human pancreas found higher levels of CCK1R mRNA (copy number of 395), but did not establish the specific cell of origin of this signal (17).

A study by Murphy *et al.* (56) more recently demonstrated the direct activation of isolated human pancreatic acinar cells in response to physiological concentrations of CCK, by measuring oscillatory increases in cytosolic calcium concentrations and subsequent enzyme secretion *in vitro.* This is the most convincing evidence supporting the hypothesis that pancreatic secretion can be mediated through direct action of CCK on pancreatic acinar cells, as well as its likely stimulation of intrapancreatic nerves (56).

In contrast, there have been many reports demonstrating the indirect action of CCK to stimulate pancreatic enzyme secretion. Studies in human and rodents have showed that cholinergic vagal activation is an important pathway for CCK to stimulate pancreatic enzyme secretion (45). Substantial evidence also supports the presence of this receptor on intrapancreatic neurons and on abdominal branches of the vagus nerve in several species (58). Indeed, CCK1R on vagal afferent fibres has been shown *in vivo* to mediate pancreatic enzyme secretion (45).

In addition to effects on secretion, CCK can exert trophic and proliferative effects on the pancreas mediated by the CCK1R. The essential contribution of CCK1R for pancreatic regeneration following pancreatectomy or pancreatic duct ligation and the importance of CCK for normal pancreatic growth has also been reported in rats (8, 50, 53, 60). Conversely, studies in mice and guinea pigs deficient in CCK peptide and CCK1R have demonstrated that CCK is not a required growth factor for the murine pancreas (43, 73).

In endocrine pancreas, CCK stimulates the release of insulin (34, 35), and CCK1R has been detected in human insulin- and glucagon-secreting cells (55). In human gallbladder, CCK1R expression has been directly demonstrated on smooth muscle cells, where it is responsible for mediating gallbladder contraction (76).

3. Tools for study

a. Molecular constructs

Mouse, rat and human wild type CCK1R cDNA clones can be purchased from GeneCopoeia (www.genecopoeia.com). Human CCK1R cDNA clone in pcDNA3.1+ vector and N-terminal HA tagged CCK1R in pcDNA3.1+ vector are available from UMR cDNA Resource Center, Missouri University of Science and Technology (www.cdna.org). Human CCK1R cDNA in lentiviral vector pReceiver-Lv105 is available from GeneCopoeia.

b. Antibodies

Polyclonal antibodies raised against peptide epitopes within the amino-terminal and carboxyl-terminal tail regions of the CCK1R are available from many commercial sources, such as Santa Cruz Biotechnology (sc 16172, sc 16173, sc 33220), Pierce Antibodies (Thermo Scientific) (PA3-116, PA5-32692, PA5-32693, PA1-36144, PA1-31121), Novus Biologicals (NBP1-00743, NB100-2805, NB100-60552, NLS3291), Abcam (ab77269, ab28627, ab140762, ab75153, ab140805, ab115287, ab14441), Acris Antibodies (AP01210PU-N, AP02079SU-N, AP02079SU-S, AP02080SU-N, AP02080SU-S, AP02080SU-S, AP16373PU-N, AP16597PU-N, AP20083PU-N, AP20084PU-N, BP2199, EUD3801, SP4663P), LifeSpan BioSciences (LS-A3291, LS-A3293, LS-A820, LS-A822, LS-C120637, LS-C54624, LS-C22102, LS-C177096, LS-C157607, LS-C54623, LS-C151628, LS-C151629, LS-C128134, LS-C128132, LS-C128131, LS-C89020, LS-C35919), and Merck Millipore (AB9514).

c. Antagonists

Several peptide and non-peptidyl antagonists of the CCK1R have been developed for the treatment of a variety of gastrointestinal disorders. These compounds have been successfully used for *in vitro* and *in vivo* studies. The CCK1R antagonists that are commercially available include the following: devazepide (L-364,718) (pIC_{50} 9.7, Tocris Bioscience, cat no. 2304; Sigma-Aldrich, cat no. D3821; Santa Cruz Biotechnology. cat no. sc-203562), SR 27897 (pIC_{50} 8.3, Tocris Bioscience, cat no. 2190), lorglumide (pIC_{50} 6.7-8.2, Sigma Aldrich, cat no. L109), loxiglumide (pIC_{50} 6.5, Sigma Aldrich, cat no. SML0130), and CR 1409 (pIC_{50} 7.86, Phoenix Pharmaceuticals, cat no. 069-08).

d. Transgenic mice

A specific strain of rat known as OLETF rats (Otsuka Long Evans Tokushima Fatty) which naturally lacks CCK1R expression was characterized at the Tokushima Research Institute (Otsuka Pharmaceutical, Tokushima, Japan) (36, 37, 74). A $CCK1R^{-/-}$ mouse lacking exon 3 which encodes for a portion of the third transmembrane segment and the second intracellular loop including the “ERY” motif was developed by Kopin *et al.* (41). This animal has been shown to exhibit reduced inhibition of food intake, but normal body weight. Suzuki *et al.* have generated a $CCK1R^{-/-}$ mouse lacking exon 2 (71), which exhibits decreased biliary and pancreatic secretion.

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