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CCK(-like) and receptors: Structure and phylogeny in a comparative perspective

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ABSTRACT

Cholecystokinin (CCK) and gastrin are regulatory peptides in vertebrates. Their homologues are widely present in metazoan animals, in form of cionin in tunicates, neuropeptide-like protein 12 in nematodes and sulfakinin (SK) in arthropods. CCK(-like) peptides exert diverse physiological effects through binding their corresponding receptors, which are important members of the hormone-binding G-protein-coupled receptors.

In this paper, CCK(-like) peptides and receptors are reviewed in a comparative way at levels of molecular structure, physiological functions and phylogeny. CCK signalling system is widely involved in the regulation of satiety, gastric acid secretion, pancreatic secretion, anxiety and memory processes in vertebrates. Its counterpart SK in arthropods is also found with similar functions on regulation of satiety and gastrointestinal motility. Co-evolution of peptide and receptor has been recognized through metazoans. The CCK(-like) receptors seem to be evolved from a common ancestor based on the phylogenetic analysis, with species-specific events in arthropods. In addition, tetraploidization has been brought up to study the evolution of receptors. There are 2 receptors in chordates and nematodes, whereas, the number of sulfakinin receptor varies in arthropods from 0 to 2. We discussed here that the presence or absence of the SK signalling system is likely to be related to feeding behaviour.

1. Introduction

Cholecystokinin (CCK) and gastrin are regulatory peptides with both endocrine and neurotransmitter functions in vertebrates, especially in mammals (Rehfeld et al., 2007). They exert diverse interesting physiological activities through specific membrane bound receptors, CCK receptors (CCKRs), which are member of the rhodopsin G-protein coupled receptor (GPCR) superfamily (Dufresne et al., 2006). Homologues of both peptides CCK/gastrin and their receptors have been widely found in a large number of animals, including CCK/gastrin in vertebrates, neuropeptide-like protein 12 (NLP-12) in nematodes (Janssen et al., 2008) and sulfakinin (SK) in arthropods (Nachman et al., 1986a,b). Thus, the CCK signalling system represents a good example of co-evolution of neuropeptides and their receptors. In this review, we overviewed the CCK(-like) peptides and CCK(-like) receptors in a comparative way. First, the homology of CCK(-like) peptides was discussed based on their sequence and functions. Second, the CCK(-like) receptors were compared at levels of molecular structure and phylogenetic analysis as well as their ligand specificity. In addition, the evolution of CCK(-like) receptors among metazoan animals was investigated.

2. CCK(-like) peptides

2.1. Sequence

CCK and gastrin share a common carboxyamidated C-terminal tetrapeptide sequence, WMDFamide, which constitutes the minimal structure necessary for receptor binding and biological activity, although potencies of both peptides depend upon their N-terminal extensions (Dufresne et al., 2006). CCKs are expressed as peptides of various lengths including 58, 39, 33 and 8 residues, each containing a sulfated tyrosine residue (Eysselein et al., 1990). Gastrins are processed to mature products with 34 and 17 amino acid residues in length (Dockray et al., 2001). The identity of the sequence necessary for biological activity suggests that CCK and gastrin have evolved from a common ancestor (Dockray, 1977; Larsson and Rehfeld, 1977), which is mainly based on information obtained by immunochemical methods and comparative physiology (Dimaline and Dockray, 1994; Dockray, 1977; Larsson and Rehfeld, 1977; Vigna, 1986). In the past years, the gene, cDNA and/or peptide structures of CCK/gastrin-related peptides have

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been identified throughout the metazoan animals. This now makes it possible to consider the CCK/gastrin phylogeny using solid molecular information.

Caerulein in the frog *Xenopus laevis* (Hoffmann et al., 1983) and cionin in the tunicate *Ciona intestinalis* (Johnsen and Rehfeld, 1990; Thorndyke and Dockray, 1986) were identified to be homologues of the CCK/gastrin in and next to vertebrates. They both terminate with the same WMDFamide sequence. Later, their corresponding receptors were cloned and characterized (Schmitz et al., 1996; Sekiguchi et al., 2012; Williams et al., 1988). Cionin possesses sulfated tyrosines at positions 6 and 7 from the C-terminus (Johnsen and Rehfeld, 1990), which is unique in the series of CCK(-like) peptides.

In insects and nematodes, distant relatives of CCK/gastrin have also been identified as sulfakinin (SK) and neuropeptide-like protein 12 (NLP-12), respectively. Initially, a C-terminal-amidated and tyrosine-sulfated neuropeptide leucosulfakinin is isolated from the cockroach *Leucophaea maderae* (Nachman et al., 1986a,b), with C-terminal sequence YGHMRFamide. Subsequently, genes coding peptides with the same C-terminal sequence have been found from many other insect species (Meyering-Vos and Müller, 2007a,b; Nichols et al., 2009). In the nematode *Caenorhabditis elegans*, NLP-12 (also called CK) is identified as the endogenous ligand of the "CCK receptor" with C-terminal sequence YRPLQFamide (McVeigh et al., 2006; Janssen et al., 2008).

Fig. 1 depicts the amino acid sequences of representative prepropeptides of CCK, gastrin, cionin, SK and NLP-12. Notably, insect SK prepropeptide contains two SK peptides with YGHMRF in the C-terminus and three NLP-12 peptides are found in the nematode prepropeptide (Fig. 1A). The peptides all have the conserved Tyr and Phe residues and share same residues within phylum (Fig. 1B). Peptide position within the precursor is conserved across bilaterians for a given peptidergic system (Mirabeau and Joly, 2013) and here for CCK/SK/NLP-12, it is near the C-terminus of the precursor. Phylogenetic analysis by Janssen et al. (2008) demonstrates that nematode CKs, arthropod SKs and the vertebrate CCK/gastrin form separate clades, with cionin the most closely related to CCK/gastrin, which is consistent to the phylogeny of their receptors. Sekiguchi et al. (2012) propose that the CCK/gastrin family is essentially conserved in both invertebrates and vertebrates and that cionin and vertebrate CCK/gastrin are derived from a common ancestor. For more evolutionary information, please refer to the review by Johnsen (1998) (Table 1).

2.2. Functions

CCK is secreted in the gastrointestinal tract and can exert an endocrine effect via receptors in the brain or a paracrine effect via receptors in the gut (Bi and Moran, 2002; Kennedy et al., 1999; Nachman et al., 1997). In humans, CCK is reported to induce satiety, slow down gastrointestinal motility, stimulate secretion of pepsinogen, inhibit gastric acid secretion by the stimulation of the production of fundic somatostatin, stimulate gallbladder contraction, and induce endocrine and exocrine pancreatic secretion

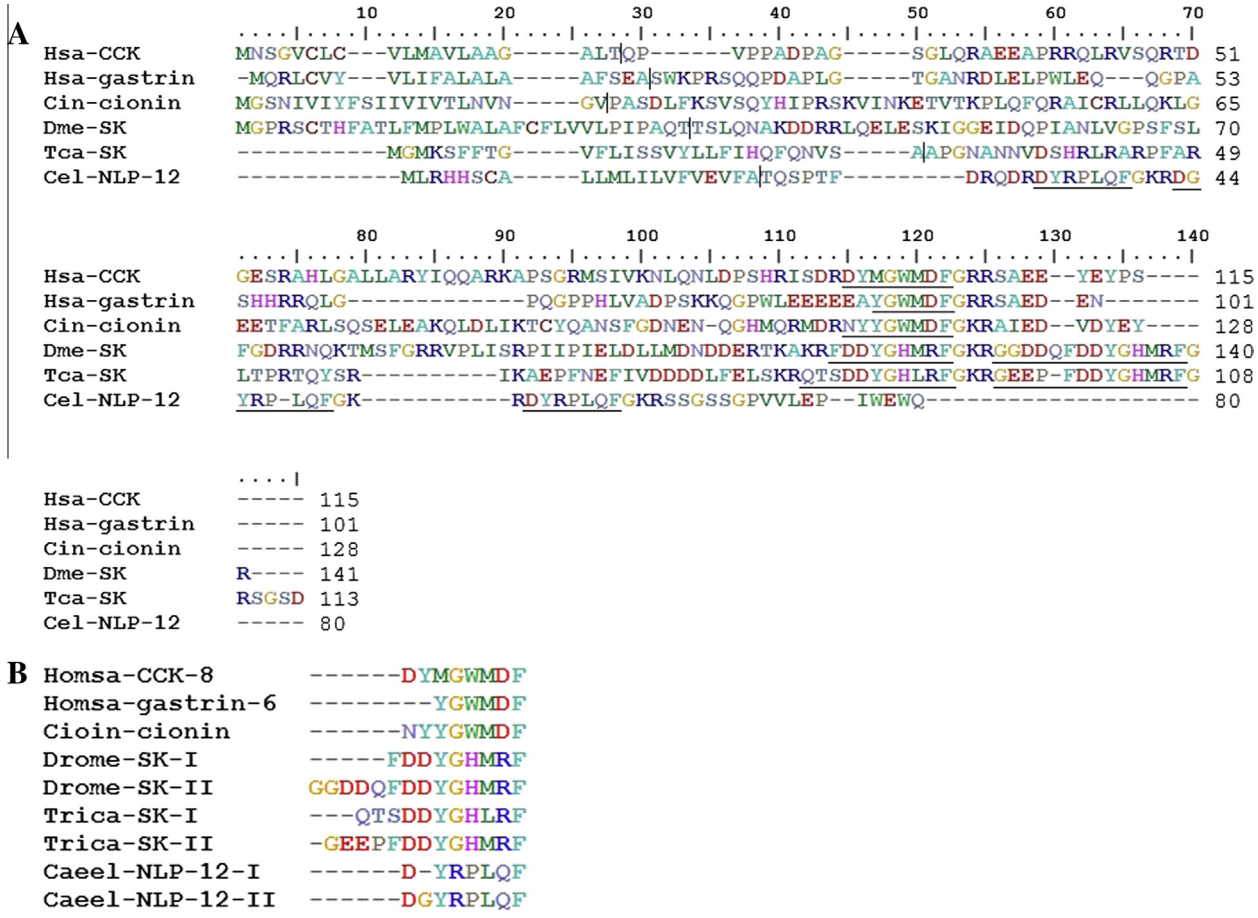

Fig. 1. Alignment of six CCK(-like) prepropeptides (A) and their corresponding biologically active peptides (B). Sequences are precursors of human CCK (Has-CCK, CAG47022.1), human gastrin (Has-gastrin, NP_000796.1), *Ciona intestinalis* cionin (Cin-cioin, CAA48884.1), *Drosophila melanogaster* SK (Dme-SK, AAF52173.2), *Tribolium castaneum* SK (Tca-SK, EFA04708.1) and *Caenorhabditis elegans* NLP-12 (Cel-NLP-12, CCD67953.1). Each amino acid residue is given a unique colour, which has no scientific meaning. Dash represents gap. The putative cleavage site of the signal peptide is indicated by a black vertical bar. The amino acids of biologically active peptides in (B) are also underlined in (A). Peptides nomenclature is with five-letter code according to Coast and Schooley (2011).