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Neuropeptidergic signaling in the nematode *Caenorhabditis elegans*

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Abstract

The nematode *Caenorhabditis elegans* joins the menagerie of behavioral model systems next to the fruit fly *Drosophila melanogaster*, the marine snail *Aplysia californica* and the mouse. In contrast to *Aplysia*, which contains 20,000 neurons having cell bodies of hundreds of microns in diameter, *C. elegans* harbors only 302 tiny neurons from which the cell lineage is completely described, as is the case for all the other somatic cells. As such, this nervous system appears at first sight incommensurable with those of higher organisms, although genome-wide comparison of predicted *C. elegans* genes with their counterparts in vertebrates revealed many parallels. Together with its short lifespan and ease of cultivation, suitability for high-throughput genetic screenings and genome-wide RNA interference approaches, access to an advanced genetic toolkit and cell-ablation techniques, it seems that this tiny transparent organism of only 1 mm in length has nothing to hide. Recently, highly exciting developments have occurred within the field of neuropeptidergic signaling in *C. elegans*, not only because of the availability of a sequenced genome since 1998, but especially because of state of the art post genomic technologies, that allow for molecular characterization of the signaling molecules. Here, we will focus on endogenous, bioactive (neuro)peptides and mainly discuss biosynthesis, peptide sequence information, localization and G-protein coupled receptors of the three major peptide families in *C. elegans*.

Keywords: Nematode; *Caenorhabditis elegans*; Neuropeptide; Insulin; FMRFamide-like peptide; *flp*; Neuropeptide-like protein gene; *nlp*; G-protein coupled receptor

Contents

Abbreviations: cGMP, 3′,5′-cyclic guanosine monophosphate; 5-HT, serotonin; AC, adenylyl cyclase; ACE, angiotensin-converting enzyme; ACh, acetylcholine; CAPS, Ca^{2+}-dependent activator protein for secretion; CELPC2, *C. elegans* proprotein convertase 2; CHO, Chinese hamster ovary; CPE, carboxypeptidase E; CNC, caenacins; DAG, diacylglycerol; DCV, dense core vesicle; FaRP, FMRFamide-related peptide; *flp*, FMRFamide-like peptide gene; GABA, γ-aminobutyric acid; GC, guanylate cyclase; GIRK, G-protein-regulated inward-rectifier K^+ channel; GPCR, G-protein coupled receptor; HEK, human embryonic kidney; HPLC, high performance liquid chromatography; IP_3, 1,4,5-trisphosphate; *ins*, insulin-like peptide gene; KPC, kex2/subtilisin-like proprotein convertase; PAL, peptidyl hydroxyglycine α-amidating lyase; PAM, peptidylglycine α-amidating monooxygenase; PC, proprotein convertase; PHM, peptidylglycine α-hydroxylating monooxygenase; PIP_2, phosphatidylinositol 4,5-bisphosphate; RIA, radioimmunoassay; RNAi, RNA interference; SV, synaptic vesicle; NEP, neprilysin; *nlp*, neuropeptide-like protein gene

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1. Introduction

Nematodes include major parasites of livestock, plants and humans in addition to free-living species such as the model organism *Caenorhabditis elegans*. The nervous system is exceptionally well defined in *C. elegans* and contains about one-third of all somatic cells. These 302 neuronal cells with 5000 synapses probably dominate a significant portion of gene circuits involved in regulatory behaviors vital to the worm's survival. Obviously, worms display a significantly less complex behavior than vertebrates. Despite the fact that *C. elegans* has a quite simple anatomy of only 959 somatic cells, it displays diverse behaviors like chemotaxis, thermotaxis, oxygen sensing, osmotic avoidance, associative learning, etc. Genome-wide comparison of predicted *C. elegans* genes with their counterparts in vertebrate nervous systems revealed many striking parallels (Bargmann, 1998; The *C. elegans* Sequencing Consortium, 1998). The major neurotransmitter biosynthetic machinery, release mechanisms and receptors are conserved. Like all other metazoan organisms, *C. elegans* uses small molecule neurotransmitters such as acetylcholine (ACh), γ-aminobutyric acid (GABA) and nitric oxide (NO); excitatory amino acids such as glutamate; and biogenic amines such as octopamine, tyramine, serotonin (5-HT) and dopamine (Brownlee and Fairweather, 1999) which are packaged into synaptic vesicles (Gasnier, 2000) and are released by exocytosis (Weimer and Jorgensen, 2003; Scalettar, 2006). In addition to these small molecule neurotransmitters, the *C. elegans* genome encodes a wide variety of bioactive peptides, which can be subdivided into three major families according to their conserved motifs. The best studied neuropeptide group in nematodes is the FMRFamide-like peptide (*flp*) gene family. A second family encloses the *ins* genes which encode insulin-like peptides, and finally, peptides without sequence resemblance with FMRFamide or insulin are derived from the so-called neuropeptide-like protein (*nlp*) genes.

Furthermore, heterotrimeric GTP-binding protein (G-protein) coupled second messenger pathways are highly conserved

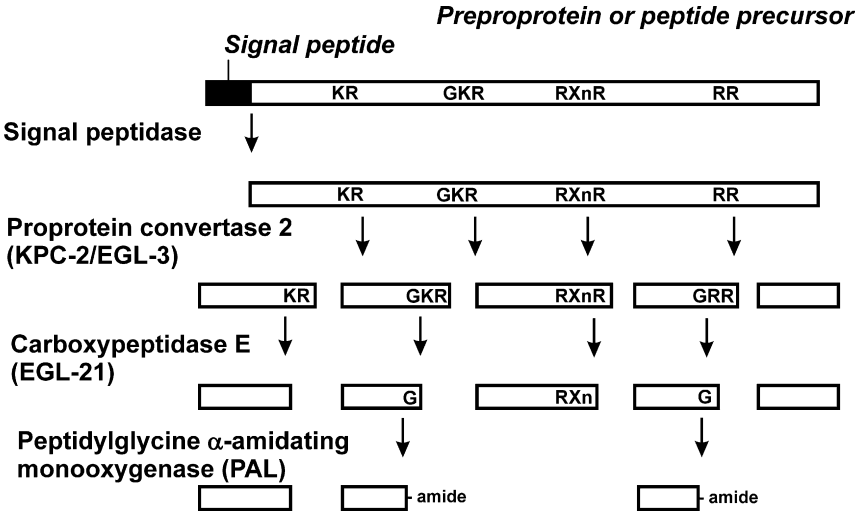

Fig. 1. Schematic representation of the neuropeptide processing pathway. A typical proprotein (neuro)peptide precursor contains an aminoterminally located signal peptide sequence that drives translocation of the precursor into the secretory pathway. The signal peptide is cleaved off by the specific action of a signal peptidase in the lumen to the endoplasmatic reticulum. Next, proprotein convertases (PCs) cleave the remaining part of the precursor at specific cleavage sites composed of basic amino acids like lysine-arginine (KR), arginine-arginine (RR) or arginine-X*n*-arginine (RX*n*R) where *n* is 2, 4, 6 or 8. Carboxypeptidases trim the carboxyterminal basic amino acids from the intermediate peptides after PC-cleavage. Finally, the carboxyterminal glycine residue, if present, is converted into an amide by peptidyl glycine α-amidating monooxygenase. This post-translational modification is a common feature for all secreted, bioactive peptides.