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More neuropeptides in *C. elegans*

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Abstract

A genome-wide scan has revealed multiple conserved groups of neuropeptide genes in the nematode *Caenorhabditis elegans*

Significance and context

Much synaptic signaling in the nervous system is facilitated by specialized peptidergic neurotransmitters called neuropeptides. Neuropeptides function in neurotransmission primarily by modulating synaptic signaling through other, small-molecule, neurotransmitters, and exert their function through seven-span transmembrane receptors, although a sodium channel that can be directly gated by the neuropeptide FMRF has been identified in the snail *Helix lucorum*. Neuropeptides thus appear also to act as fast neurotransmitters.

Molecular and biochemical studies have established that the neuropeptides comprise a large and diverse group of signal molecules, but the molecular mechanisms underlying neuropeptide-mediated synaptic transmission remain largely elusive. The nematode *Caenorhabditis elegans*, with its simple nervous system and completely sequenced genome, lends itself to a systematic analysis of neuropeptide function. A remarkable feature of this animal pertinent to such an investigation is that synaptic connectivity has been deciphered in unprecedented detail by serial sectioning and electron microscopy. In addition, many neuropeptides have already been identified in *C. elegans*, demonstrating that neuropeptide signaling operates in the worm nervous system.

Key results

Nathoo and co-workers set out to search for more neuropeptide genes in the *C. elegans* genome. Two different classes of neuropeptide genes had been described by previous studies in the worm: genes for FMRF-like proteins (*flp*), with some 23 members, and 37 insulin-related genes. Are these all? The authors note two observations that hint at the existence of more. First, there are many more putative neuropeptide receptor genes (about 130) in the *C. elegans* genome. Second, specialized dense-core synaptic vesicles (the sites of neuropeptides) that are not immunoreactive for any of the known neuropeptide families are found at nematode synapses.

To identify novel neuropeptide genes in *C. elegans*, Nathoo *et al.* first carried out similarity searches of the nematode protein database, using known neuropeptide sequences as probes. This approach returned just two novel neuropeptide-like proteins (NLPs). The limited success of the similarity search underlines the peculiar structure of neuropeptide genes: most encode many related neuropeptides, which renders them invisible to simple BLAST searches. For a neuropeptide gene to be picked up by BLAST, it would have to encode multiple unrelated neuropeptides. To overcome this limitation, the authors used PATTERNFIND, an algorithm that can scan for the existence of a defined amino-acid pattern within a protein. To filter the output of PATTERNFIND, they established a set of criteria that a *bona fide* neuropeptide would have to fulfill. This analysis was indeed more productive, and resulted in the identification of 32 putative *nlp* genes including the two (*nlp-1* and *nlp-2*) previously identified.

In summary, the 32 novel *nlp* genes identified are distributed between 11 families, on the basis of the presence of conserved motifs, and encode 151 total putative neuropeptides. For many of these newly identified neuropeptide genes, a reciprocal search of GenBank revealed the existence of close relatives in other species, which further validates the screening strategy and suggests conservation in synaptic signaling mechanisms. To identify the sites of action of the novel neuropeptides, Nathoo *et al.* generated transgenic lines for each of the genes identified with reporter green fluorescent protein fused to the neuropeptide gene. As expected, many are expressed extensively in the nervous system, indicating a function in synaptic signaling. Some are also expressed during early embryonic stages and might have a function in development.

Reporter's comments

Identification of the complete set of neuropeptide genes in a simple animal model such as *C. elegans* allows for precise deciphering of their biological function in the context of the whole organism. The nematode has a simple nervous system of just 302 neurons yet this nervous system gives rise to a remarkably elaborate array of behaviors and environmental responses. Some of these have already been shown to involve neuropeptide-facilitated neurotransmission, such as social 'clumping' behavior. The powerful genetics tools (for example, RNAi, genetic knockouts and suppression analysis) available in *C. elegans* should now assist a comprehensive investigation of peptidergic synaptic signaling.

The work also demonstrates that a combinatorial approach to mining and extracting information from genome sequence databases can be more productive than using any single tool. Although algorithms and web-based search engines exist that will summon a plethora of individual bioinformatics tools to scrutinize genomic sequences, automated genome annotation is, most of the time, not that thorough and sometimes even erroneous. Manual inspection is therefore advisable and likely to yield highly relevant information.

Table of links

References

1. Nathoo AN, Moeller RA, Westlund BA, Hart AC: Identification of neuropeptide-like protein gene families in *Caenorhabditis elegans* and other species. Proc Natl Acad Sci USA. 2001, 98: 14000-14005. 0027-8424