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Oct-GnRH, the first protostomian gonadotropin-releasing hormone-like peptide and a critical mini-review of the presence of vertebrate sex steroids in molluscs

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ABSTRACT

In protostome and deuterosome invertebrates, neurosecretory cells play major roles in the endocrine system. The optic glands of cephalopods are indicators of sexual maturation. In mature octopuses, optic glands enlarge and secrete a gonadotropic hormone. A peptide with structural features similar to that of vertebrate gonadotropin-releasing hormone (GnRH) was isolated from the octopus, *Octopus vulgaris*, and was named oct-GnRH. The discovery of oct-GnRH has triggered structural determinations and predictions of other mollusc GnRH-like peptides in biochemical and *in silico* studies. Interestingly, cephalopods studied so far are characterized by a single molecular form of oct-GnRH with a C-terminal -Pro-Gly-NH_2 sequence, which is critical for gonadotropin-releasing activity in vertebrates. Other molluscan GnRH-like peptides lack the C-terminal -Pro-Gly-NH_2 sequence but have -X-NH_2 or -Pro-Gly although all protostome GnRH-like peptides have yet to be sequenced.

In marine molluscs, relationships between GnRH-like peptides and sex steroids have been studied to verify the hypothesis that molluscs have vertebrate-type sex steroid system. However, it is currently questionable whether such sex steroids are present and whether they play endogenous roles in the reproductive system of molluscs. Because molluscs uptake and store steroids from the environment and fishes release sex steroids into the external environment, it is impossible to rule out the contamination of vertebrate sex steroids in molluscs. The function of key enzymes of steroidogenesis within molluscs remains unclear. Thus, evidence to deny the existence of the vertebrate-type sex steroid system in molluscs has been accumulated. The elucidation of substances, which regulate the maturation and maintenance of gonads and other reproductive functions in molluscs will require rigorous and progressive scientific study.

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1. Introduction

In protostome and deuterosome invertebrates, neurosecretory cells play major roles in the endocrine system. Insects and crustaceans possess a well-developed endocrine system, such as the corpus allatum, the prothoractic gland, the X organ-sinus gland system and Y organ, and the androgenic gland. These cells control molting, metamorphosis, body color change, and gonadal maturation. The optic glands of cephalopods (octopuses, squids, and cuttlefishes), a pair of small pale yellowish spheres situated on the stalks joining the large optic lobes to the rest of the central nervous system (CNS), are indicators of sexual maturation. *Octopus vulgaris* normally breeds during the second year as the terminal event in the life cycle; the females lays and cares for eggs without feeding, expiring shortly after the eggs hatch (Wells and Wells, 1977). A secretion from the optic glands regulates the sexual maturation and the feeding behavior detailed below. When the optic glands are removed after the eggs have been laid, the female octopus stops brooding her eggs, begins feeding again, and subsequently lives for a prolonged period with an enlarged body (Wodinsky, 1977). Implantation of glands from sexually mature individuals to immature recipients induces precocious maturation (Wells and Wells, 1977). Optic gland implants between both sexes are equally effective, suggesting that the factor is not sex-specific (Wells and Wells, 1977). Interspecific and intergeneric implants from other octopods are also effective but not from decapods, cuttlefishes, or squids (Wells and Wells, 1977). Secreted substances

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from optic glands enhance the synthesis of yolk protein in the octopus follicles (Wells and Wells, 1977).

Sexual maturation of the octopus is also controlled by light. When the optic nerves are cut in immature female octopuses, the optic glands enlarge with color change from pale yellow to red, and the ovaries increase 100-times in size within a month (Wells and Wells, 1959). The optic glands are innervated by the optic gland nerve from the subpedunculate lobe in the posterior part of the supraesophageal brain mass. Lesions of the subpedunculate lobe or cutting of the optic tract cause enlargement of optic glands and subsequently the enlargement of gonads (Wells and Wells, 1959). Unilateral central lesions or optic nerve sectioning cause optic gland enlargement on the operated side only but appear to be as effective in determining gonad enlargement as bilateral treatments (Wells and Wells, 1959). This result leads to the conclusion that enlargements of optic glands are not under hormonal but nervous control (Wells and Wells, 1959). Maturation of gonads is determined by secretion from optic glands, which is normally controlled by an inhibitory nerve supply of the optic gland nerve from the subpedunculate lobe. Two synaptic contacts in fibers of the optic gland nerve, axo-axonal and axo-glandular, were observed in the immature optic gland of the octopus. The axo-axonal synapses are deconstructed and axo-glandular synaptic contacts remain in the mature optic glands (Froesch, 1974). This microscopic observation leads to the hypothesis that the optic gland secretory cells require an excitatory nervous stimulus for hormone production via an axo-glandular synapse (Froesch, 1974), which is inhibited by the axo-axonal synapse (Froesch, 1974). Di Cosmo et al. reported that Phe-Met-Arg-Phe-NH_2 (FMRF-amide)-like immunoreactivity seen in the optic gland in turn suggests axo-axonal synapses on chicken gonadotropin releasing hormone 1 (cGnRH1)-immunoreactive fibers (Di Cosmo and Di Cristo, 1998). Somewhat discrepant results about properties of optic gland hormones have been reported. For instance, the lack of a well-developed rough endoplasmic reticulum and secretory vesicles (Froesch and Mangold, 1976), and the presence of lipid inclusions and mitochondria with tubular cristae (Lofts and Bern, 1972) in the optic glands are all characteristic of a steroidogenic tissue. In the optic gland of *Sepia*, the presence of a well-developed rough endoplasmic reticulum and secretory granules in the glandular cells suggested synthesis and release of proteins (Richard, 1971). Extracts from the matured optic glands induce ^{14}Leu uptake and protein synthesis *in vitro* in *Octopus* follicles, suggesting the presence of gonadotropic hormone (Wells and Wells, 1977). A 4–5 kDa gonadotropic and mitogenic factor has been partially characterized from extracts of optic glands and hemolymph of the cuttlefish, *Sepia officinalis* (Koueta et al., 1992). The activity of this fraction was totally destroyed in boiling water and partially impaired by trypsin digestion, suggesting that it is a peptide, but not a steroid (Koueta et al., 1992). The presence of similar activity with 4–5 kDa in the hemolymph suggests that it is a peptide hormone (Koueta et al., 1992). Although the characteristics of the optic gland secretion have been studied in detail, the structural elucidation of the GnRH1-like immunoreactive substance and hormone like material was impeded until the study by Iwakoshi et al. (2002).

1.1. Discovery of octopus gonadotropin-releasing hormone like peptide (oct-GnRH)

Iwakoshi and colleagues isolated a dodecapeptide with structural features similar to those of vertebrate GnRHs from the brains of an octopus and named it oct-GnRH (Iwakoshi et al., 2002). GnRHs from chordate species are decapeptides, so that the -Asn^2-Tyr^3- residues of oct-GnRH are inserted. Oct-GnRH appears to satisfy the structural requirements for gonadotropin-releasing activity in vertebrates, such as the Glu^1- residue at the N-terminus, -His^4- and -Ser^6- residues, and -Pro^{11}-Gly^{12}-NH_2 at the C-terminal region except for the two residues insertion (Millar et al., 1989). In fact, oct-GnRH displays luteinizing hormone-releasing activity in the anterior pituitary cells of the Japanese quail *Coturnix coturnix* (Iwakoshi et al., 2002).

The structural organization of the precursor protein of oct-GnRH is similar to that of vertebrate GnRHs. The precursor consists of a signal peptide, a peptide hormone sequence, a -Gly-Lys-Arg-sequence, and a GnRH-associated protein (GAP)-like sequence (Iwakoshi et al., 2002). A partial cDNA characterized by an exactly similar sequence to the oct-GnRH precursor has been cloned from the cuttlefish *S. officinalis*, and its expression has been detected in the brain and ovary (Di Cristo et al., 2009a). The open reading frame of the cDNA cloned from the central nervous system (CNS) of swordtip squid *Uroteuthis edulis*, is 80.5% similar to that of oct-GnRH in nucleotide sequence (Onitsuka et al., 2009) (Fig. 1a). The amino acid sequences of *Sepia* and *Uroteuthis* GnRH are identical to oct-GnRH (Fig. 1b).

Discovery of oct-GnRH in *Octopus* has triggered structural determinations and predictions of other molluscan GnRH-like peptides. Genomes and EST databases of several molluscs are also useful to the studies. Novel precursors of GnRH-like peptides have been reported (Table 1). GnRH-like peptides encoded on these precursors have a well conserved N-terminal sequence of oct-GnRH, however, C-terminal structures are diverse. The C-terminal -Pro-Gly-NH_2 structure that is critical to gonadotropin-releasing activity in vertebrates is not found in these peptides. The Pro residue is not conserved. The -X-Gly-Gly- sequence in the precursor protein is necessary to produce the C-terminal -X-Gly-NH_2 in the mature peptide. Therefore, the matured forms of GnRH-like peptides will be undecapeptides with C-terminal -X-NH_2, and/or dodecapeptides with C-terminal -X-Gly (see Table 1). In fact, cg-GnRH has two molecular forms (cg-GnRH-a with -Pro-NH_2 and cg-GnRH-G with -Pro-Gly at the C-terminus), which were determined with mass spectrometry (MS) and MS/MS analyzes (Bigot et al., 2012). Thus, only cephalopods studied so far have a single molecular form of oct-GnRH with C-terminal -Pro-Gly-NH_2 although all protostome GnRH-like peptides have yet to be sequenced. It is noteworthy that the precursors of molluscan GnRH-like peptides except for oct-GnRH (Table 1) are characterized by a tribasic cleavage site at the C-terminal such as -Arg-Lys-Arg-. If a point mutation was to occur in a triplet codon CGX of the first Arg to GGX, the -Arg-Lys-Arg- sequence would switch to the -Gly-Lys-Arg- sequence that contains a donor Gly residue of the C-terminal -Gly-NH_2 formation. Excellent reviews and papers on molecular evolution of invertebrate GnRH-like peptides and GnRH-related peptides have been published (Roch et al., 2011, 2014; Lindemans et al., 2011; De loof et al., 2012; Grimmelikhuijzen and Hauser, 2012; Sun et al., 2012; Kawada et al., 2013; Di Cosmo and Polese, 2013).

The distribution of oct-GnRH and the expression of oct-GnRH mRNA have been investigated in the brain, optic gland, heart, and oviduct and oviducal gland by immunohistochemistry and *in situ* hybridization (Iwakoshi-Ukena et al., 2004). Immunoreactive neuronal cell bodies are observed in the subpedunculate lobe, which controls the optic-gland activity (Iwakoshi et al., 2002). Oct-GnRH mRNA-expressing cell bodies are also detected in the subpedunculate lobe (Iwakoshi et al., 2002). Oct-GnRH immunopositive neuronal fibers are stained in the subpedunculate lobe, and some may reach the optic gland via the optic tract. Oct-GnRH immunoreactive cell bodies and fibers in the posterior olfactory lobe and immunopositive fibers in the optic gland are detected (Iwakoshi et al., 2002).

Although the perikarya of stellate cells of the optic gland are immunostained by the oct-GnRH antiserum (Iwakoshi et al., 2002), oct-GnRH mRNA-positive cells are not detected in the optic

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