Gonadotropin-Releasing Hormone Receptors: Where Did They Come From?

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It's a long way from Amphioxus,
It's a long way to us,
It's a long way from Amphioxus
To the meanest human cuss.
It's good-bye, fins and gill-slits,
Welcome, lungs and hair!
It's a long, long way from Amphioxus,
But we all came from there.

Pope, 1921 (sung to the tune of "It's a Long Way to Tipperary," Judge/Williams).

Pope got it right, although amphioxus is a slimy ancestor to acknowledge. But what does this beast have to tell us about our origins? In this issue, Tello and Sherwood (1) propose that in amphioxus, the most basal chordate, four GnRH receptors are present: two that sit at the base of the invertebrate lineage and two at the base of the vertebrate lineage.

Amphioxus, also known as the lancelet, grows to about 5 cm, has a dorsal nerve cord and other vertebrate characteristics including segmented muscles, a tail, and pharyngeal slits. Amphioxi live in the sand in tropical regions and, despite their evolutionary importance, are now primarily a food source. The simultaneous presence of two GnRH receptor lineages in this organism is remarkable, because it hints that amphioxus might contain similar kinds of evidence about other aspects of early vertebrate evolution.

For a ligand to act, it must have a cognate receptor, and one of the most important ligands in vertebrates is GnRH1. The hypothalamus secretes GnRH1, the peptide that controls reproduction in all vertebrates. GnRH was predicted to exist in 1950 (2), but because there are only minute amounts, and the peptide has modified N and C termini, it was difficult to isolate. Twenty years later, it was structurally identified, and 12 yr after that, in 1984, the gene encoding GnRH was first described for humans (3) and rats (4). Seven years later, the first cDNA encoding GnRH in a nonmammalian species was identified in a teleost fish, leading to subsequent discoveries in that same species of three distinct genes encoding three different GnRH decapeptides and localized in spatially distinct brain areas (5). The discovery of a second form of GnRH in humans and the associated phylogenetic analysis showed that the three GnRH gene families then known formed a tidy tree, suggesting a common origin via gene duplication and that then a subsequent loss of one form was the likely evolutionary path to extant GnRH forms (6). Since then, the lamprey GnRH form has been fitted into a fourth category of GnRH molecules and the protostomian GnRHs placed into yet another lineage (7). In most species, GnRH forms are localized to particular brain areas. But GnRH peptides cannot function without cognate receptors. And the two to three GnRH forms are not matched to specific receptor types in any vertebrate where they have been identified, but rather each GnRH can bind to either of the two receptors expressed in most vertebrates.

Consequently, the GnRH receptor identities and functions have been somewhat complex to understand and place into reliable families (*cf.* Ref. 8). These receptors seem to have been duplicated and in some cases acquired new functions during evolution. But the Tello and Sherwood (1) report suggests that at the dawn of vertebrates, things might have been more distinct. Amphioxus (*Branchiostoma floridae*) is the most basal chordate, but it is also classified as an invertebrate. This schizophrenic origin is supported by results showing that amphioxus has four GnRH receptors: two paralogous pairs with one phylogenetically grouped with the vertebrate GnRH receptors and the other grouped with the invertebrate (octopus) GnRH-like receptors (Fig. 4 in Ref. 1). Even more interesting, the vertebrate GnRH forms, GnRH1 and GnRH2, activate the vertebrate-type GnRH receptors, and correspondingly, an octopus GnRH-like peptide and related receptor for insect adipokinetic hormone (AKH) induced inositol phosphate pathway turnover in one of the two amphioxus receptors. So it appears that there is functional conservation from amphioxus through the vertebrate lineage. The authors infer that the mollusk GnRH-like receptor was lost somewhere in the vertebrate lineage and that one of the vertebrate-like receptors gave rise to all subsequent vertebrate GnRH receptors.

Independently, Chambery *et al.* (9) identified a putative GnRH in amphioxus using reverse-phase chromatography. The

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peptide sequence is identical to that of mammalian GnRH (pGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2), and the highest concentrations were found at a time just before seasonal spawning. Perhaps most remarkably, Chambery *et al.* (9) showed that the amphioxus GnRH could induce LH release from rat pituitary, similar to induction by mammalian GnRH. This is all the more remarkable because there is no known pituitary in amphioxius, suggesting that GnRH served to regulate reproduction even before the appearance of a reproductive axis. So, at the dawn of vertebrates, a GnRH ligand and four putative receptors were in place for natural selection to act.

Taken together, these two papers show the ancient origins of GnRH and suggest that amphioxus may be an interesting place to search for other phylogenetic origins.

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