Chemical cues for sea lamprey migration

Andrew Dittman

During the past century, the sea lamprey colonized the Great Lakes of North America and decimated the commercial fishing industry. The isolation and characterization of a migratory pheromone from the sea lamprey expands options for control of this invading species.

Pheromonal communication between members of a species is critical in the life history, development, physiology and behavior of many animals. Pheromones, as first defined by Karlson and Luscher, are "substances that are excreted to the outside by an individual and received by a second individual in which they release a specific reaction, for example, a definite behaviour or developmental process"[1]. For years, pheromonal compounds that elicit migration, metamorphosis and reproductive behavior have been exploited successfully as management tools for controlling a number of native and invasive agricultural pests. Although considerable progress has been made in identifying the chemical nature and biological function of pheromones for a number of insect species[2,3], chemical ecologists have made less progress in identifying pheromones for vertebrates that may be useful in controlling invasive species. In this issue of *Nature Chemical Biology*[4], Peter Sorensen, Thomas Hoye and colleagues report the identification and characterization of a migratory pheromone of the sea lamprey (*Petromyzan marinus*) and take a large step toward developing a pheromone-based control effort for this extremely destructive invasive fish.

The sea lamprey is a primitive jawless fish that has a fascinating anadromous life history involving distinct freshwater and saltwater phases. Lamprey hatch in freshwater streams and spend the majority of their life as tiny filter-feeding larvae. After a period of typically 4–6 years, they undergo a dramatic metamorphosis to a free-swimming form that migrates to the ocean or large lakes. As adults, sea lamprey attach themselves to the bodies of other fish with their oral disk and rasp through the skin with sharp teeth to feed on body tissues and fluids (often resulting in death of the parasitized fish). After 1–2 years at sea, lamprey mature and migrate back into freshwater streams to spawn and die.

Sea lamprey are native to the Atlantic Ocean but entered the Great Lakes system of North America through man-made ship canals and

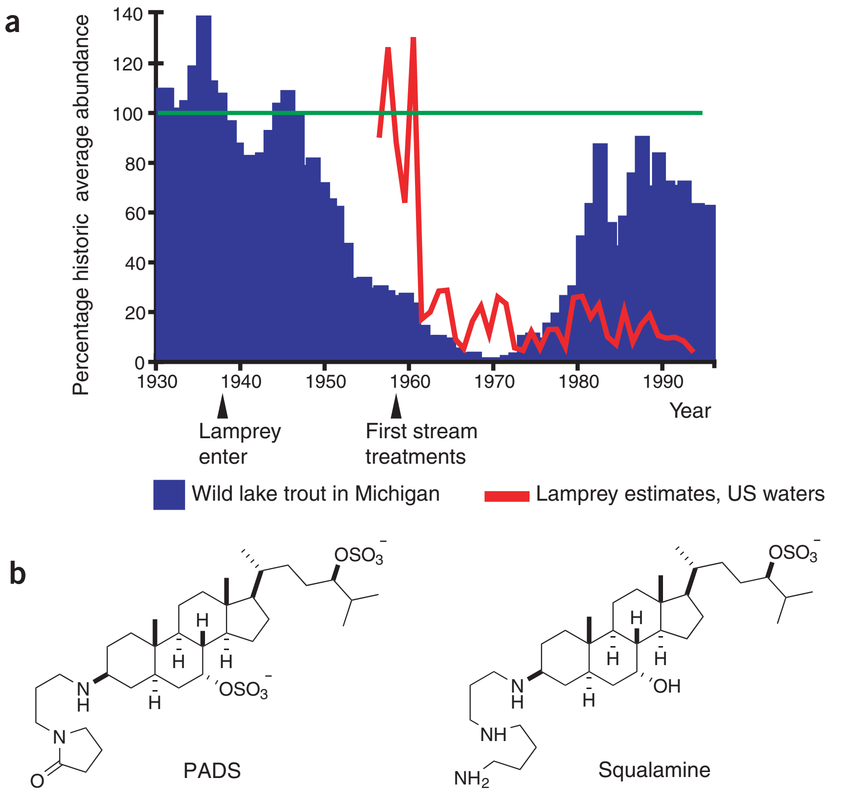

Figure 1 Sea lamprey migratory pheromones and invasive species control. (**a**) Example of the effects of lamprey invasion and lamprey control measures on lake trout abundance. Data represent abundance of wild lake trout as a percentage of the 1929–1943 average and historical estimates of lamprey abundance in Lake Superior. Lamprey numbers declined dramatically after control measures were initiated. Pheromone-based control offers the potential for further suppression of lamprey numbers in the Great Lakes. Figure from the Great Lakes Fishery Commission (Ann Arbor, Michigan); reprinted with permission. (**b**) Comparison of the structures of petromyzonamine disulfate (PADS) and squalamine, an antibiotic found in sharks.

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locks during the early 1900's. Rather than migrate to sea at metamorphosis, these invasive lamprey exploited the rich fishery resources of the Great Lakes during their parasitic phase, feeding on all large fish, but especially devastating the commercially valuable lake trout and salmon populations. For example, after sea lamprey entered Lake Superior, wild lake trout abundance declined to less than 10% of the historical average (**Fig. 1a**)[5]. The initiation of a variety of control measures, including treating spawning rivers with lampricides, trapping, installing passage barriers and releasing sterilized males, has reduced sea lamprey populations in the Great Lakes (**Fig. 1a**), but lamprey continue to cause major ecological damage. The use of pheromones for biological control of sea lamprey has been proposed for a number of years[6], and the recent identification of a potent male sex pheromone that is strongly attractive to reproductive females has offered new hope for the efficacy of the approach[7].

In addition to using reproductive pheromones, sea lampreys have long been known use natural odor cues to detect and select streams for spawning. Unlike salmon that migrate back to their natal stream to spawn using learned odor cues, maturing lamprey migrate into any stream with appropriate spawning and rearing habitat. Extensive field and laboratory tests have demonstrated that maturing lamprey use a highly attractive migratory pheromone released by stream-resident larval lampreys to identify appropriate spawning streams[8]. Subsequent work by Sorensen and his colleagues indicated that larval lamprey release a unique bile acid, petromyzonal sulfate (PS), which is a potent odorant and highly attractive to migrating adults[9]. However, these studies also suggested that water in which larvae were held was more attractive than equivalent concentrations of petromyzonal sulfate alone, suggesting that there might be additional components to the migratory pheromone.

In the present study, Sorensen and colleagues sought to identify all of the individual components of the sea lamprey migratory pheromone. Using a two-choice maze to test for odor attraction, they first demonstrated that the pheromone blend could be stably extracted from larval holding water. The extract was then fractionated by HPLC, and individual fractions were screened for olfactory activity and behavioral responses of maturing adults. They identified three fractions with potent olfactory activity that, when combined, demonstrated an attractive pheromonal activity almost equivalent to larval holding water. Finally, using a large-scale purification of 8,000 liters of water containing ~35,000 larvae, they identified three sulfated sterol derivatives with pheromonal activity.

The most potent compound was a new disulfated aminosterol derivative, petromyzonamine disulfate (PADS, **Fig. 1b**), an extremely potent odorant which elicited olfactory and behavioral responses at concentrations as low as 10^{-13} M. The authors confirmed its identity by independent synthesis. Interestingly, this compound also shows considerable structural similarity to squalamine[10] (**Fig. 1b**), a unique antimicrobial agent discovered in sharks, perhaps suggesting that the earliest vertebrate pheromones may have evolved from such compounds. Two other sulfated sterols, petromyzolsterol disulfate (PDDS) and the previously identified compound PS were also identified. The authors demonstrated that the mixture of these three compounds was a more potent attractant than any of the components alone. While the authors could not rule out the presence of other low-abundance compounds, a strong case is made that the tripartite mixture reproduces the observed signaling behavior of larval holding water.

These exciting results should provide new tools for managers to be used as part of integrated programs to control the spread of sea lamprey in the Great Lakes. Although it remains to be demonstrated that these pheromones can be used effectively on a large scale, analogous approaches with insects suggest that lamprey migratory pheromones, perhaps used in conjunction with reproductive pheromones, may be useful in bait-and-kill traps, mating disruption or for luring lamprey into inhospitable streams. Ironically, these compounds may ultimately also be useful for recovery and reestablishment of other lamprey species that are threatened or endangered by attracting them to spawn in underutilized habitat. In summary, the identification of the sea lamprey migratory pheromones is an exciting step forward, and these compounds hold extraordinary promise for use in invasive species control.

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New light on an open-and-shut case

Dean R Madden

In the brain, neurotransmitter-receptor binding represents the moment of stereochemical recognition in which one neuron senses the signal sent by another. Submillisecond time-resolved FTIR spectroscopy now provides a first glimpse of the generative protein-ligand interactions that lead to glutamate receptor ion channel activation.

While most intracellular neuronal signals are carried by transmembrane electrical impulses, fast cell-to-cell communication in the brain is primarily chemical: neurotransmitters released by one cell diffuse across a narrow cleft and bind to receptor ion channels on the surface of another. The resulting transmembrane electrical current constitutes the final step in the process of synaptic transmission. Since the ligand-binding site is typically far from the transmembrane pore of these channels, the opening of the pore requires an intricately choreographed series of allosteric conformational changes, whose early stages have so far eluded direct observation. In this issue, Jayaraman and colleagues present the first direct evidence that the molecular recognition process begins with a series of reciprocal 'handshake' interactions[1].

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