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Review

Exploiting the physiology of lampreys to refine methods of control and conservation ☆

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A B S T R A C T

Lampreys (order: Petromyzontiformes) represent one of two extant groups of jawless fishes, also called cyclostomes. Lampreys have a variety of unique features that distinguish them from other fishes. Here we review the physiological features of lampreys that have contributed to their evolutionary and ecological success. The term physiology is used broadly to also include traits involving multiple levels of biological organization, like swimming performance, that have a strong but not exclusively physiological basis. We also provide examples of how sea lamprey traits are currently being used or investigated to control invasive populations in the Great Lakes, such as reduced capacity to detoxify lampricides, inability to surmount low barriers or dams, and sensitivity to several lamprey-specific chemosensory pheromones and alarm cues. Specific suggestions are also provided for how an improved knowledge of lamprey physiological traits could be exploited for more effective conservation of native lampreys and lead to the development of next generation sea lamprey control and conservation tools.

Contents

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Introduction

Lampreys (order: Petromyzontiformes) are one of two extant groups of jawless fishes known as cyclostomes. There are at least 41 recognized lamprey species (Riva-Rossi et al., 2020; Docker and Hume, 2019; Potter et al., 2015), with the majority distributed in the Northern Hemisphere. All lampreys begin life as burrow-dwelling, blind, filter-feeding larvae, which are traditionally referred to as ammocoetes (Clemens, 2019). This stage typically lasts 3–7 years, with larvae growing to lengths of approximately 180 mm (Dawson et al., 2015). The final year of the larval stage is usually characterized by the accumulation of lipid reserves needed to sustain a 3–4 month non-trophic metamorphosis into juveniles or young adults (Manzon et al., 2015; Youson, 2003) (Fig. 1).

Lamprey metamorphosis is a true metamorphosis characterized by major changes in anatomy and physiology (Youson, 2003). Morphological changes include formation of well-developed eyes, the loss of the oral hood and its replacement with a multi-toothed oral disc (also called a suctorial disc) and a serrated piston-like tongue,

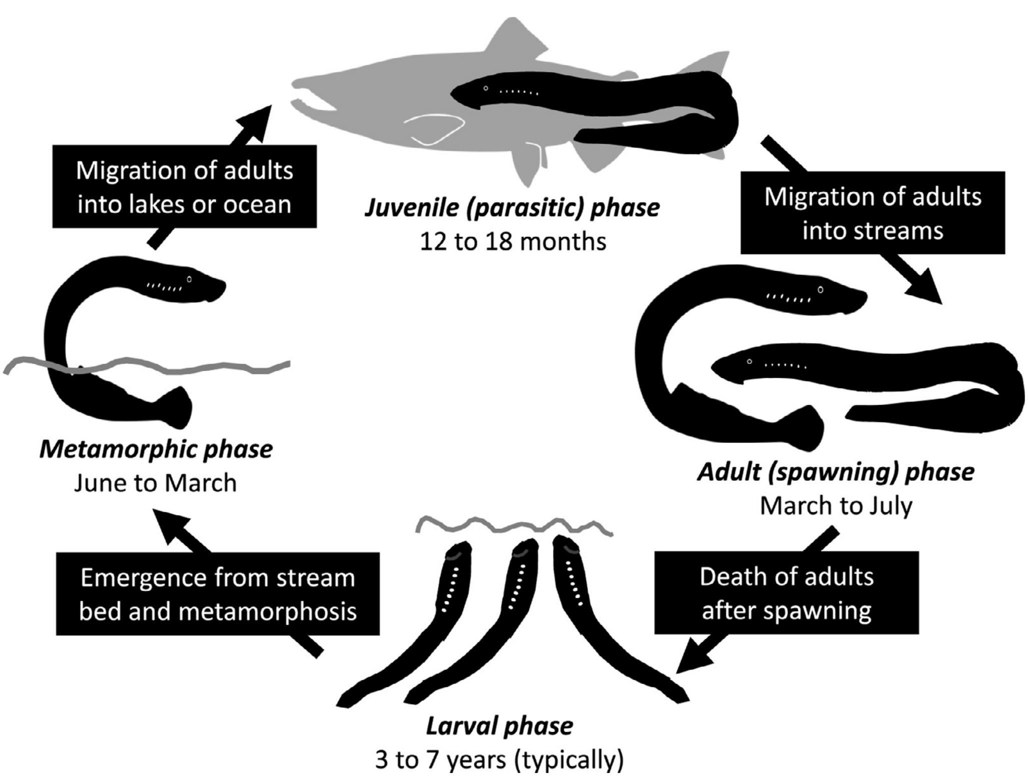

Fig. 1. The sea lamprey life cycle annotated with approximate duration and timing of each life stage.

and development of larger dorsal fins (Renaud, 2011; Rovainen, 1996). Depending upon the species, the juvenile lampreys adopt a parasitic feeding mode, in which the animals feed on the blood and/or tissues of bony fishes and even elasmobranchs (Renaud, 2011; Wilkie et al., 2004) or remain non-trophic, maturing and proceeding directly to the adult, reproductive phase of their life cycle within 6–10 months of metamorphosis (Docker and Potter, 2019; Docker, 2009). There are 19 parasitic species, 10 of which migrate to sea to feed (although some have produced freshwater-resident populations) and nine that are entirely restricted to freshwater (Riva-Rossi et al., 2020; Docker and Potter, 2019; Potter et al., 2015; Renaud, 2011). Non-parasitic species evolved from parasitic lampreys; in some cases, the parasitic species is still extant, and the non-parasitic and parasitic "paired species" overlap in distribution and are morphologically and genetically indistinguishable as larvae (Docker and Potter, 2019; Docker, 2009). The remaining "unpaired" non-parasitic species without an obvious extant parasitic ancestor are often referred to as "relict species" (Docker and Potter, 2019; Potter et al., 2015).

At least 12 lamprey species are classified as at risk in at least part of their range due to factors such as habitat degradation, poor water quality, and barriers to movement (Maitland et al., 2015). The sea lamprey (*Petromyzon marinus*) is simultaneously an invasive species in the North American Great Lakes and of conservation concern in parts of its native range in Europe (Maitland et al., 2015). The Great Lakes is also home to four native lamprey species: northern brook lamprey (*Ichthyomyzon fossor*), silver lamprey (*I. unicuspis*), chestnut lamprey (*I. castaneus*), and American brook lamprey (*Lethenteron appendix*). Where these species overlap in distribution with sea lamprey, they are vulnerable to sea lamprey control efforts (Neave et al., 2021). In the Pacific Northwest and California, populations of the Pacific lamprey (*Entosphenus tridentatus*) are threatened by habitat degradation, barriers to migration, and climate change (Clemens et al., 2017; Moser et al., 2021). Pacific lamprey and other anadromous species historically supported harvests that are no longer sustainable (Almeida et al., 2021). The inability to harvest lampreys represents an economic and cultural loss to Indigenous groups in the region (Almeida et al., 2021). In some cases, recovery of native lampreys is needed to both restore ecosystem function and satisfy reciprocity needs amongst Indigenous peoples that value lampreys and other animals for food, medicine, and ceremonial purposes (Maine, 2020; Kitson and Moller, 2008).

Sea lamprey first appeared in the Great Lakes in the mid to late 19th century and were established there by the 1930s (Marsden and Siefkes, 2019; Eshenroder, 2014). The sea lamprey invasion, exacerbated by other factors, resulted in catastrophic damage to several fisheries (Brant, 2019; Marsden and Siefkes, 2019; Smith and Tibbles, 1980; Lawrie, 1970). Populations of sea lamprey were subsequently brought under control using an integrated pest management program initiated by the Great Lakes Fishery Commission that included chemical control using lampricides 3-trifluoromethyl-4-nitrophenol (TFM) and niclosamide, barriers to spawning migration, and traps to remove spawning adults (Lennox et al., 2020; Marsden and Siefkes, 2019; Wilkie et al., 2019; Siefkes, 2017; Hlina et al., 2021). An overarching, perhaps underappreciated, aspect of the sea lamprey control program was that it exploited "unique" or taxon-specific aspects of the sea lamprey's physiology to minimize the impact on non-target species (Siefkes, 2017). Because lampreys, as only one of two extant groups of jawless fishes (and the only ones found in freshwater), diverged from other vertebrates over 450 million years ago, they possess both ancestral vertebrate traits not retained by later diverging vertebrates (so-called "primitive" traits) and lamprey-specific derived

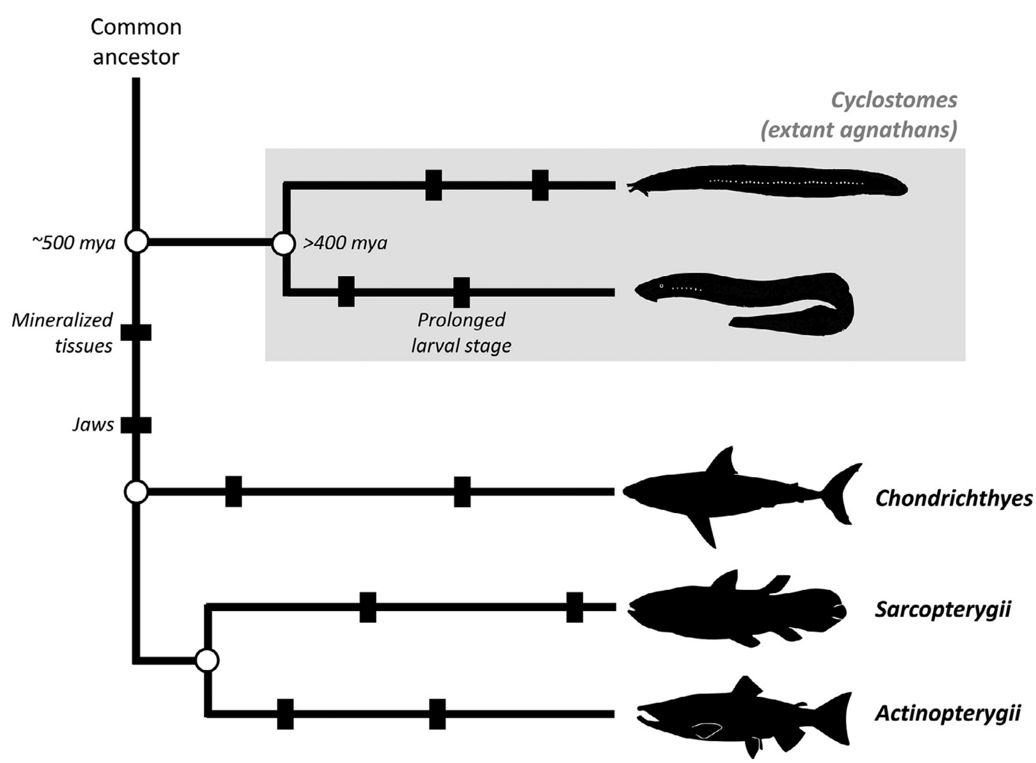

Fig. 2. Evolutionary relationship between cyclostomes and jawed vertebrates, and the origin of cyclostome features that distinguish them from other fishes. The cyclostomes (hagfishes and lampreys) are a monophyletic group and are thus more closely related to each other than to other lineages. However, the two cyclostome lineages diverged >400 million years ago (mya) and have subsequently acquired (e.g., a prolonged larval phase in lampreys) or lost (e.g., compound eyes in hagfishes) traits within their separate lineages. Similarly, the gnathostomes, which includes the Chondrichthyes (cartilaginous fishes), the Sarcopterygii (lobe-finned fishes and tetrapods), and the Actinopterygii (ray-finned fishes, including teleosts and non-teleost fishes such as gars, bowfin, and sturgeons) all last shared a common ancestor with cyclostomes ~500 mya, and have separately gained and lost many traits over time. Lampreys therefore possess many unique features that can be exploited for conservation and control. The appearance of a few specific (labelled) and generalized (unlabelled) lineage-specific traits are shown.

traits (see below). We suggest that focusing on and understanding these aspects of the physiology of lampreys can be used to develop "next generation" methods of lamprey control and contribute to the conservation and rehabilitation of lamprey species that are at risk due to anthropogenic habitat disturbances.

In this synthesis, we first discuss some of the key ancestral and derived features of lamprey physiology that have contributed to their evolutionary success and that have been exploited for control. Herein, the term physiology is used broadly to also include traits involving multiple levels of biological organization, like swimming performance, that have a strong but not exclusively physiological basis. Because this is not an exhaustive review of anatomy and physiology, readers are referred to other reviews that provide insights into these topics (Manzon et al., 2015; Sower, 2015; Wilkie, 2011a, b; Renaud et al., 2009; Bartels and Potter, 2004; Youson, 2003; Youson, 1980). Specific ideas are provided on how an improved knowledge of lamprey physiology could be exploited for both more effective sea lamprey control and for the conservation of native lampreys. Emphasis is placed on defining features that distinguish lampreys from jawed (gnathostome) fishes.

The "primitive features of lampreys

Lampreys and hagfishes, the only other extant group of agnathans, possess most of the hallmarks of vertebrate evolution, including pronounced cephalization, specialized sense organs, and a multi-lobed brain, as well as complex circulatory, respiratory, endocrine, excretory, and digestive systems (Docker and Potter, 2019; Manzon et al., 2015; Weinrauch et al., 2015). However, their lack of jaws, paired fins, and other gnathostome features has led many scholars to describe these early diverging vertebrates as "primitive," which implies that hagfishes and lampreys are less evolved than other vertebrates. Similarly, the cyclostomes are sometimes referred to as "living fossils" (e.g., Docker et al., 2015) due to their morphological similarity to fossils from the distant past (Lidgard and Love, 2018).

However, not all lamprey traits are "primitive." Indeed, lampreys have also acquired novel (derived) traits since diverging from other vertebrates over 450 million years ago (Miyashita et al., 2021; Miyashita et al., 2019; Heimberg et al., 2010) (Fig. 2). For example, lamprey life history is a patchwork of ancestral and derived characters (Evans et al., 2018). The characteristic multi-stage life cycle, which includes a prolonged larval stage, a true metamorphosis, a parasitic/non-parasitic juvenile stage, and a sexually mature adult stage, is not an ancestral lamprey trait. Although the fossil record shows that multi-stage life cycle had evolved by the Upper Cretaceous (Chang et al., 2014), Miyashita et al. (2021) provided compelling evidence that the ammocoete larval stage is a derived trait and does not represent the ancestral vertebrate condition. Evans et al. (2018) suggested that selection for dramatically different ammocoete and juvenile stages made a transitional metamorphosis necessary. The ammocoete larval form became specialized to take advantage of newly hospitable freshwater environments, which permitted a "safe haven" from predators, while the juvenile form became fully specialized to take advantage of the newly diversifying jawed fish fauna (Docker and Potter, 2019).

Therefore, in this review, we use the term "ancestral" rather than "primitive." Ancestral traits are those that have been inherited from the common ancestor of a clade and exist relatively unchanged in the evolutionary descendants of that ancestor (Kardong, 2006); in contrast, derived traits are those that appear within a clade but do not appear in a common ancestor (Kardong, 2006). Which lamprey traits are ancestral and which are derived is still somewhat ambiguous for several reasons. First, the precise evolutionary relationships between cyclostomes and other vertebrates remain an area of active research (Miyashita et al., 2021; Miyashita et al., 2019). Second, unlike anatomical traits that are preserved in the fossil record (albeit poorly so in the case of soft-bodied organisms like lampreys), physiological traits must be inferred based on circumstantial anatomical, geological, and ecological evidence. Third, there remains uncertainty on how to integrate physiological traits into phylogenetic analyses, particularly derived traits that may confer some adaptive value (Janvier, 2007; Garland et al., 2005; Huey, 1987). With recent developments such as the molecular clock approach and more precise analytical procedures for resolving phylogenies, the last two points are becoming less of an issue, though there still remains much work to be done in characterizing the last common ancestor of cyclostomes and gnathostomes.

From a practical standpoint, we posit that both ancestral and derived traits, as long as they are lamprey-specific, can be considered in the development of more specific and effective management and conservation strategies for lampreys. Control methods that target lamprey-specific vulnerabilities (or, better yet, *sea* lamprey-specific vulnerabilities) will, by definition, have few or no negative effects on non-target species. This approach could also be used in developing novel strategies to conserve vulnerable native lamprey populations. In both cases, a better understanding of the physiology of lampreys is required to develop new and improve current modes of control and conservation measures for native lampreys. Thus, rather than restrict our discussion to ancestral ("primitive") features, we will focus on features of lamprey physiology, both ancestral and derived, as well as those of uncertain evolutionary origin, that distinguish them from non-target fishes in their ecosystem.

Adaptations that allowed sea lamprey to colonize the Laurentian Great Lakes

Sea lamprey possess several developmental, behavioral and physiological characteristics that likely facilitated their successful establishment and spread across the Great Lakes. These include high fecundity, a prolonged larval (ammocoete) stage, and wide tolerance ranges to environmental stressors including variations in salinity and osmolarity, and temperature, which enabled their spread and survival across a broad geographical range (Morman et al., 1980; Farmer et al., 1977). Juvenile sea lamprey in marine environments are commonly observed at depths up to 200 m (Holčík et al., 2004; Mateus et al., 2021), with observations recorded as deep as 1,000 m (Beamish, 1980; Haedrich, 1977). Prey are readily accessible in the Great Lakes where the average depths range from 19 m in Lake Erie to 147 m in Lake Superior, in which the maximum depth is approximately 406 m.

Life history

The prolonged larval stage, spent burrowed in soft, silty substrate of rivers and streams, allows sea lamprey to thrive in these habitats despite the sometimes limited food resources of nursery streams and the presence of predators (Evans et al., 2018; Hansen et al., 2016; Morman, 1987). The absence of natal homing by upstream migrating adult sea lamprey also appears to be beneficial because it allows sea lamprey to choose spawning streams based on discharge, temperature, and the presence of migratory chemosensory cues secreted by larval lampreys (Li et al., 2018a; Waldman et al., 2008; Fine et al., 2004; Sorensen and Vrieze, 2003). In contrast to chemosensory cues which attract migratory fishes to their natal streams to spawn, larval pheromones provide a good indicator of contemporary rather than historical larval rearing habitat. Larval pheromones, which are partially comprised of bile salts and fatty acids, have been demonstrated to elicit behavioral responses among heterospecific lampreys (Clemens et al., 2010; Fine et al., 2004). In the early stages of the sea lamprey invasion, migratory pheromones secreted by native lampreys may have attracted sea lamprey to suitable spawning rivers.

Sea lamprey are also highly fecund; a single adult female can produce 50,000 to 100,000 eggs (Docker et al., 2019; Gambicki and Steinhart, 2017; Johnson, 1982). In contrast, fecundity of the native lamprey species in the Great Lakes averages only 1,200 to 19,000 eggs per female (Docker et al., 2019). Previous estimates suggested that up to 90% of sea lamprey eggs are fertile and could successfully hatch (Manion and Hanson, 1980); however, success in wild populations may be much lower, with up to 86% of the eggs disappearing from the redd (Smith and Marsden, 2009).

Parasitism traits

A key to the success of the sea lamprey invasion was the ability of juvenile sea lamprey to parasitize a broad range of hosts. More than 50 marine and freshwater host species have been reported for sea lamprey (Quintella et al., 2021; Renaud and Cochran, 2019); this lack of host specificity means that sea lamprey are less likely to be impacted from changes in the distribution and abundance of individual host species. The serrated piston-like tongue of sea lamprey is able to pierce the hide of numerous fish species enabling them to feed on a wide range of bony fishes in the Great Lakes, including lake trout (*Salvelinus namaycush*), walleye (*Sander vitreus*), whitefish (*Coregonus clupeaformis*), burbot (*Lota lota*), suckers (*Catostomus* spp.), and lake sturgeon (*Acipenser fulvescens*) (Renaud and Cochran, 2019; Harvey et al., 2008; Swink, 2003).

Successful parasitism is aided by secretions from the buccal glands. Like the anti-coagulants of other blood-feeding animals (e.g., hirudin and draculin secreted by medicinal leeches and vampire bats, respectively; Kakumanu et al., 2019; Low et al., 2013), lampreys produce lamphredin, a mix of anticoagulants, ion channel blockers, and immune suppressors to facilitate feeding on living hosts (Xiao et al., 2012; Gage and Gage-Day, 1927).

Euryhalinity and freshwater ionoregulation

Euryhalinity is another hallmark feature of anadromous lampreys, including sea lamprey (Zydlewski and Wilkie, 2012). Sea lamprey ionoregulatory mechanisms are broadly similar to other hyperosmotic regulators in freshwater environment and hypoosmotic regulators in seawater environments (Sunga et al., 2020; Reis-Santos et al., 2008; Bartels and Potter, 2004; Ferreira-Martins et al., 2021). In anadromous populations, the transition from freshwater to seawater is enabled by a preparatory stage that begins during metamorphosis (Ferreira-Martins et al., 2021). Adults lose seawater-type ionocytes in preparation for freshwater migration and replace them with intercalated (freshwater-type) ionocytes for a characteristic hyperosmoregulatory strategy that involves uptake of Na^+ and Cl^- and high urinary flow rates (Wilkie et al., 1998; Logan et al., 1980a; Logan et al., 1980b; Read, 1968).

The retention of intercalated ionocytes by juvenile sea lamprey in freshwater likely contributed to their ability to invade and thrive in the Great Lakes. Another feature of freshwater fishes, including landlocked sea lamprey, is a lowered ion permeability of the gills due to the presence of deeper tight junctions between adjacent epithelial cells than in saltwater (Kolosov et al., 2020; Kolosov et al., 2017; Bartels and Potter, 2004; Bartels et al., 1996); Ferreira-Martins et al., 2021). However, tight junction protein composition does not appreciably differ between freshwater-acclimated juvenile and larval sea lamprey, suggesting that juveniles from landlocked populations may retain some of the characteristics that restrict ion losses by larval lamprey, which likely contributed to their propensity to thrive in the Great Lakes (Kolosov et al., 2020; Kolosov et al., 2017).

In addition to the capacity of juvenile sea lamprey to survive in freshwater, the capacity of larval lamprey to thrive in a range of water chemistries is likely important, as the concentrations of several ions (Ca^{2+}, Mg^{2+}, Na^+, Cl^-) vary substantially across the Great Lakes and their tributaries due differences in local geology, soil composition, vegetation, and other factors (O'Connor et al., 2017; Chapra et al., 2012). A key to the survival of larval lamprey is an ability to upregulate their ion transport capacity (Morris and Bull, 1968; Bull and Morris, 1967) and to reduce branchial ion permeability in more dilute waters through changes in the abundance and composition of the epithelial tight junction proteins (Kolosov et al., 2020; Kolosov et al., 2017).

Thermal physiology

The wide thermal tolerance of sea lamprey may also have factored in their ability to colonize rivers and streams throughout the Great Lakes basin. Larval sea lamprey experience temperatures that are barely above freezing in the winter, and up to the mid- to the high-20 s (°C) in the summer. Their incipient upper lethal temperature is ~31.4 °C in the laboratory (Potter and Beamish, 1975), and more recent studies demonstrate that the upper critical temperature (CT_{max}) falls between 32.5 °C and 34.4 °C, depending upon acclimation temperature (Sutherby, 2019). This tolerance to high temperatures is also reflected by the very high temperatures needed to induce heat shock protein expression, approximately 13–16 °C above ambient acclimation temperatures, in larval sea lamprey (Wood et al., 1999, 1998). The thermal niche of larval lampreys, where physiological performance is optimal, is 17.8–21.8 °C, which overlaps with the niche of many temperate water fishes (Lennox et al., 2020; Holmes and Lin, 1994). However, the capacity of *larval* sea lamprey to tolerate episodic extremes in temperature could contribute to their wide distribution in the Great Lakes. The thermal tolerance of juvenile sea lamprey was not likely a factor in their occupation of the Great Lakes, because they prefer to feed on cold-water salmonid species in the Great Lakes, such as lake trout that are generally found between 4 and 12 °C (Lennox et al. 2020).

Swim performance and behavior

The vertebral column (notochord) is positioned more dorsally in lampreys than it is in most jawed fishes, and most myotomes therefore sit below the notochord (McKenzie et al., 2007; Peters and Mackay, 1961). This structure precludes paired fins, which limits the lamprey's ability to produce thrust and to control pitch, yaw and roll, thereby limiting some aspects of swimming performance. Sea lamprey rely on anguilliform locomotion and have a relatively low cost of transport (van Ginneken et al., 2005; Tytell and Lauder, 2004; William and Beamish, 1979), partially due to their ability to pull themselves through the water by generating local regions of low fluid pressure around the body (Gemmell et al., 2015). The relatively low propulsive force generated by the lamprey swimming pattern, as well as their lower active metabolic rate and lower absolute aerobic scope, may contribute to their relatively poor aerobic exercise performance (Hanchett, 2020). Typical critical swimming speeds for upstream migrating sea lamprey are lower than for comparably-sized bony fishes ($\leq$1.5 body lengths per second for sea lamprey, and $\geq$ 2 body lengths per second for salmonids, centrarchids, and catostomids) (Crans et al., 2015; Underwood et al., 2014; Wilkie, 2011b; McKenzie et al., 2007). Field measurements indicate that migrating sea lamprey also have a lower range of speeds and mean speed than comparably-sized salmonids (McKenzie et al., 2007; Standen et al., 2004; Standen et al., 2002; Stier and Kynard, 1986). In contrast to teleosts, lampreys lack a swim bladder and must swim continuously to avoid sinking; however, their relatively lightweight cartilaginous skeleton and large lipid reserves probably provide some buoyancy (Wilkie et al. 2011a).

Though sea lamprey may not have the same critical swimming speed as migratory salmonids, mature Pacific lamprey and sea lamprey can nevertheless swim for hundreds of kilometers to reach upstream spawning locations at rates greater than 20 km per day (Hansen et al., 2016; McKenzie et al., 2007; Almeida et al., 2002). The critical swimming speed of adult sea lamprey is similar to the ground speed observed during migration, suggesting that they routinely approach their aerobic limits (Quintella et al., 2004; Beamish, 1974). Behaviorally, migrating adult lampreys also tend to swim near the bank, avoid areas with high flow, and stay near the bottom (Rous et al., 2017; Holbrook et al., 2015; McKenzie et al., 2007), all characteristics that allow lampreys to use boundary layers and take advantage of low flow areas to conserve energy. This behavior is typically followed by attachment to substrate, presumably to rest and recover (Moser et al., 2015b), something that teleost fishes cannot do.

Lampreys use their oral sucker to attach to substrate in high-velocity areas (Kirk et al., 2016; Holbrook et al., 2015; McKenzie et al., 2007; Quintella et al., 2004). Some anadromous species (e.g., Southern Hemisphere species, Pacific lamprey) have elaborated this behavior to climb vertically using a combination of oral sucker attachment coordinated with powerful cycles of axial undulation (Kemp et al., 2009). This mode of movement, while potentially energetically costly, may be required to navigate natural obstacles during upstream migration (Kemp et al., 2009). Adult sea lamprey and European river lamprey (*Lampetra fluviatilis*) climb wetted ramps with studs using anguilliform swimming (Reinhardt and Hrodey, 2019; Vowles et al., 2017; D'Aguiar, 2011). Studded ramps could be a promising approach to selectively remove or pass lampreys when optimized; passage efficiencies of adult sea lamprey in 6 m × 1 m × 1 m enclosures constructed in a Michigan stream reached 98% (Hume et al., 2020).

Both mature and larval sea lamprey are capable of rapid recovery from the metabolic and acid-base imbalances incurred by exhaustive exercise compared to a typical teleost fish. In mature adults, muscle phosphocreatine and adenylates recovering within 1 h, and substantial lactate clearance, glycogen restoration, and recovery of muscle CO_2 occurring within 4 h or more (Boutilier et al., 1993; Tufts, 1991). Rapid blood pH recovery, and eventual reestablishment of acid-base balance, relies on excretion of protons across the body surface (Wilkie et al., 1998).

As in adults, exhaustive exercise leads to significant depletion in phosphocreatine and glycogen, lactate accumulation, and metabolic acidosis in larval sea lamprey (Wilkie et al., 2001). Larvae recovering from exhaustive exercise show a five-fold increase in oxygen uptake, rapid rates of proton excretion, lactate elimination, and glycogen replenishment, in order to rapidly restore metabolic homeostasis (Wilkie et al., 2001). Though lamprey larvae generally have a sedentary lifestyle, the capacity for rapid recovery from exercise could be important for burrowing and/or burst swimming to escape predators (Wilkie et al., 2001).

Existing control methods that exploit the novel physiological features of sea lamprey

Selective barriers and traps

The lack of paired fins and reliance on anguilliform swimming makes sea lamprey relatively poor leapers compared to teleosts (Reinhardt et al., 2009; McKenzie et al., 2007; Youngs, 1979). Purpose-built lamprey barriers may incorporate a jumping pool for migratory fish passage (Lavis et al., 2003; Hunn and Youngs, 1980), but even low barriers will impede non-jumping fishes and other lamprey species (Dodd et al., 2003; Hunn and Youngs, 1980). While purpose-built barriers are often successful to preventing lamprey passage, this is not always the case (Chase, 1996; McAuley, 1996), suggesting that there are some aspects of lamprey swimming physiology that do not translate well between the lab and the field. Future habitat restoration efforts in the Great Lakes region will need to balance the benefits of increased habitat connectivity with increased lamprey access (Milt et al., 2018; McLaughlin et al., 2013), and will likely benefit from ongoing research into adult sea lamprey behavior and swimming performance (Reinhardt and Hrodey, 2019; Holbrook et al., 2015; Bravener and McLaughlin, 2013; Quintella et al., 2009; McLaughlin et al., 2007; Quintella et al., 2004).

Barriers, especially those built specifically to block sea lamprey, are often equipped with traps that are selective for adult sea lamprey during the upstream migration (Miehls et al., 2020; McCann et al., 2018; Schuldt and Heinrich, 1982). Traps are placed along the shore, and water from upstream of the barrier is passed through traps to increase attraction and entry into the trap (Zielinski et al., 2019). Captured sea lamprey can be marked and released to estimate adult sea lamprey abundance (Adams et al., 2021), sterilized and released for control purposes (Bravener and Twohey, 2016), used for research, or culled. In streams that are difficult to treat with lampricides and where adult sea lamprey density is low, removal of adult sea lamprey or release of sterile males may reduce reproduction and serve as a control method (Johnson et al., 2021 - a; Miehls et al., 2021). Exploiting and integrating multiple aspects of sensory physiology (discusssed below) may allow for more efficient and selective barriers and traps.

Sensitivity to lampricides

A novel feature of lamprey physiology is their relatively poor capacity to detoxify the lampricide TFM, a phenolic compound which is applied to streams infested with larval sea lamprey, but normally has minimal effects on non-target organisms (Wilkie et al., 2019; Hubert, 2003; Howell et al., 1980; Hlina et al., 2021). As TFM accumulates, it interferes with oxidative ATP production by the mitochondria in a dose-dependent manner. This leads to an ATP supply–demand imbalance, and reliance on anaerobic energy reserves, including glycogen and phosphocreatine (Clifford et al., 2012; Birceanu et al., 2009; Wilkie et al., 2007). When these finite anaerobic reserves are exhausted, death ensues (Wilkie et al., 2019). Although the mechanism of TFM action is similar in sea lamprey and bony fishes, the greater tolerance of non-target fishes to TFM exposure is due to their greater ability to effectively detoxify and excrete TFM using Phase II biotransformation in the liver (Tessier et al., 2018; Hlina et al., 2017). Indeed, this more-or-less lamprey-specific effect of TFM has been the key to the success of the sea lamprey control program for more than 60 years (Wilkie et al., 2019).

A key step in the detoxification of phenolic compounds such as TFM is the addition of a glucuronide functional group to the compound, making it more water soluble and easier to excrete (Clarke et al., 1991). In the case of TFM, TFM-glucuronide is formed in a reaction catalyzed by uridine 5′-diphospho-glucuronosyltransferase (UDP-GT) (Bussy et al., 2018a,b; Kane et al., 1994; Lech and Statham, 1975). The greater sensitivity of sea lamprey to TFM appears to be due to much lower UDP-GT activity in the liver, which is about half of that observed in rainbow trout (*Oncorhynchus mykiss*) (Kane et al., 1994), and corresponds to much lower TFM-glucuronide accumulation in the tissues of TFM-exposed sea lamprey (Bussy et al., 2018a, b; Kane et al., 1994; Lech and Statham, 1975).

UDP-GT belongs to a superfamily of enzymes called UDP-glycosyltransferases that likely evolved in herbivores to detoxify toxic chemical compounds (metabolites) produced by plants (Bock, 2003). It is therefore tempting to hypothesize that many of the genes coding for the UDP-glycosyltransferase enzymes (involved in phenol metabolism) were not present or were silenced in lampreys and possibly hagfishes, which feed exclusively on blood, other bodily fluids and/or tissues for part of their life cycle. Indeed, there may have been little selective pressure to express gene(s) coding for the UDP-glycosyltransferase family of enzymes involved in the glucuronidation of phenolic or polyphenolic compounds produced by plants because host fishes will have already done so. Indeed, loss of UDP-GT activity is seen in domestic and wild cats as well as other hypercarnivorous animals such as hyenas and sea lions, which have little need to detoxify such compounds due to their diet (Bock, 2016; Shrestha et al., 2011; Court and Greenblatt, 2000).

While the hypothesis that UDP-GT is expressed at lower levels in lampreys due to the hypercarnivorous diet of the parasitic stage animals is interesting, the fact is that most of the life cycle of extant lampreys is spent in the larval stage, which are thought consume a much more varied diet consisting of plant-like algae including diatoms, detritus, and bacteria (Moore and Beamish, 1973; Manion, 1967). In fact, the larval stage is a derived trait in the lampreys. As noted above, recent analysis of a developmental series of the fossil lamprey *Priscomyzon* suggests that an ammocoete-like larval stage was absent (Miyashita et al., 2021), and, except for their small size, these fossil lampreys bear remarkable resemblance to extant juvenile or adult lampreys (Docker and Potter, 2019; Miyashita, 2018). Among modern lampreys, nonparasitism is a derived trait and, among parasitic lampreys, Potter and Hillard (1987) concluded that blood feeding is ancestral (see Docker and Potter, 2019). This may also explain why nonparasitic native lampreys are also vulnerable to TFM (Maitland et al., 2015), despite presumably having a diet where functional UDP-GT enzymes would be advantageous.

A potential flaw in the above hypothesis is that the filter-feeding larval stage likely appeared in the lamprey lineage approximately 210 million years ago (Miyashita et al., 2021), during which time the selective pressure for greater UDP-GT enzyme might have been expected to be much higher if the larvae were ingesting plant-like material such as algae and diatoms (e.g. Manion 1967; Moore and Beamish 1973). However, more recent studies on extant larval sea lamprey and American brook lamprey suggest that plant or "plant-like material" such as algae and diatoms, comprises a relatively small proportion of their diet, which is predominately organic detritus (Evans and Bauer, 2016; Mundahl et al., 2005; Sutton and Bowen, 1994). Detritus mainly represents dead plant and animal material that accumulates as debris in the sediments and/or is suspended in the water column as particulate organic matter (Bowen, 1987). This factor, along with the relatively low rates of feeding (Sutton and Bowen, 1994), may have limited the larval lamprey's exposure to toxic phenolic compounds. Consequently, the selective pressure for the evolution for a broader or more efficient suite of UDP-glycosyltransferase enzymes may have simply been insufficient.

More work is clearly needed to disentangle the underlying mechanisms and evolutionary drivers for lampreys' relative inability to detoxify TFM. Further biochemical analysis of their glucuronidation capacity compared to non-target fishes, and most importantly genomic characterization of not only the UDP-glycosyltransferase family of enzymes but other Phase 1, 2, and 3 pathways of detoxification. Such characterization will not only shed more light on TFM, as well as niclosamide, handling by lampreys, but also lead to identification of other novel traits that can be exploited to control sea lamprey.

Ongoing research to exploit novel physiological features of sea lamprey for control

Chemosensory

Conspecific and heterospecific chemical cues released by larval lampreys influence stream selection by adult sea lamprey, with more adults entering streams and tributaries containing a higher biomass of larvae (Li et al., 2018b; Wagner et al., 2006; Fine et al., 2004; Sorensen and Vrieze, 2003). The migratory cue released by larvae presumably does not benefit the larvae in the stream (but see Weaver et al., 2018), so it is hypothesized to have evolved from adults relying on larval odors (Sorensen and Stacey, 1999). Identification and synthesis of the mixture of diverse compounds released by larvae has been challenging (Li et al., 2018b; Sorensen et al., 2005). However, if the mixture can be synthesized at low cost, it could be used to redirect adult sea lamprey into areas where other lamprey control measures, such as traps or lampricides, are known to be effective.

In addition to the larval pheromone, sexually mature male sea lamprey release a diverse mixture of compounds that induces physiological and behavioral responses mainly in sexually mature females (Chung-Davidson et al., 2013a; Chung-Davidson et al., 2013b; Li et al., 2002). These pheromones have been shown to marginally increase capture of females (Johnson et al., 2015b; Johnson et al., 2013); Johnson et al., 2021 - a), and one pheromone has been registered as the first vertebrate biopesticide in the USA and Canada (Fredricks et al., 2021). When males spawn, their semen also contains a sex pheromone, spermine, that attracts sexually mature female sea lamprey (Scott et al., 2019). Like cues released by larvae, identification and synthesis of the full suite of sex pheromones has been difficult (Buchinger et al., 2015; Li et al., 2002), which has hindered full deployment of these sex pheromones. Using sex pheromones to increase trapping rates and redirect adult sea lamprey away from spawning areas continues to be active areas of research (Fissette et al., 2021).

Another means to exploit the chemical ecology of sea lamprey is to cause sensory disruption or antagonize the reception of chemical cues in the olfactory organ. When a component of the sex pheromone, 3kPZS (3-keto petromyzonol sulfate), was applied at concentrations equivalent of that released by hundreds of males, ovulating females were less likely to locate natural sources of the sex pheromone collected directly from males (Johnson et al., 2009). However, the cost of synthesizing 3kPZS is limiting to the use of this approach in sea lamprey control. A component of the migratory cue released by larval lampreys, PZS (petromyzonol sulfate), functions as a behavioral antagonist to 3kPZS (Buchinger et al., 2015). Therefore, PZS may be useful for controlling sea lamprey reproduction by disrupting mate location and thus successful reproduction (Fissette et al., 2021).

As noted above, sea lamprey attractant chemical cues are not species-specific (Buchinger and Li, 2020; Fine et al., 2004), and they appear to be conserved among most lampreys in the Northern Hemisphere (Fine et al., 2004). Sex pheromones are more specialized among lampreys than migratory cues (Buchinger et al., 2019), but some components such as PZS and 3kPZS are shared among different species (Buchinger et al., 2019; Buchinger et al., 2017). Overlap of pheromone activity among lampreys could be problematic if these compounds are used for sea lamprey control because they may disrupt migration and reproduction of native lampreys in the area (Buchinger et al., 2020). Furthermore, measuring the concentration of these chemical cues in river water could be a possible sea lamprey population assessment method, but doing so would require correcting for those compounds released by native lampreys (Fissette et al., 2021).

Larval, juvenile, and adult sea lamprey avoid chemical cues released by dead conspecifics (Fissette et al., 2021). When exposed to dead lamprey odor, larvae are less likely to leave their burrows and swim downstream (Wagner et al., 2016), juveniles are more likely to move downstream (Johnson et al., 2019), and maturing adults avoid the odor sources (Bals and Wagner, 2012). These putative alarm cues could be useful in sea lamprey control in that juveniles and adults could be pushed into traps, and larvae could potentially be inhibited from moving downstream to lentic areas where lampricide treatments are more difficult. Research continues to identify alarm cues (Dissanayake et al., 2019), and alarm cues have been shown to influence multiple lamprey species, especially in phylogenetically close species (Hume and Wagner, 2018).

Additional details on the use of sea lamprey chemosensory cues in sea lamprey control are provided in other articles in this issue (Fissette et al., 2021; Fredricks et al., 2021) and in a review by Buchinger et al. (2015).

Photosensory and vision

The eye, pineal complex, and dermal photoreceptors on the tail represent the characterized photoreceptive systems in lamprey. These systems can function independently and their role in influencing physiology and behavior varies throughout the life cycle (Binder et al., 2013; Binder and McDonald, 2008). Larvae have underdeveloped eyespots with flattened lenses that sit beneath non-transparent skin, and therefore likely have little light sensing or image forming capacity (Suzuki and Grillner, 2018). The burrowing behavior of larvae is instead mediated by dermal photoreceptors: when the tail region is exposed to light, refuge seeking movement increases (Binder and McDonald, 2008; Ronan and Bodznick, 1991). During metamorphosis to the juvenile stage, a complex image forming eye that is largely analogous to the eyes of other vertebrates erupts and develops (Morshedian et al., 2021; Fain, 2019; Suzuki and Grillner, 2018; Morshedian and Fain, 2015). Sensitivity and behavioral responses of juveniles to illumination of dermal photoreceptors decreases, likely as an adaptation to open water parasitism of fishes at all times of day (Binder et al., 2013). Adult sea lamprey migrating to spawning grounds revert to nocturnal behavior as mediated by dermal photoreceptors, not the eye (Binder and McDonald, 2008). When spawning commences, the responses of dermal photoreceptors wane and sea lamprey can be active any time of day (Walaszczyk et al., 2013; Binder and McDonald, 2008).

Sea lamprey are most vulnerable to light-mediated control interventions while migrating out of streams as juveniles and while migrating up streams to spawn. Out-migrating juveniles show positive phototaxis to low intensity light in experimental flumes (100 lux 1 m from light; Haro et al., 2020; Johnson et al., 2019) and were more likely to be captured in a lit trap relative to a non-lit trap. In the same flume experiments, high intensity light (1000 lux 1 m from light) slowed downstream transit rate. Conceivably, light could create an ecological trap for juveniles by slowing down their migration and increasing efficiency of predators that rely on visual cues and that are also attracted to light (Stamplecoskie et al., 2012). Alarm cues emitted by dead larvae increases the downstream movement of juveniles; and when alarm cue is combined with light, more juveniles move downstream and are attracted to low intensity light (Johnson et al., 2019). Catch rates of adult sea lamprey migrating upstream have also been higher in lit traps (9–100 lux) versus unlit traps when placed side-by-side (Stamplecoskie et al., 2012; Purvis et al., 1985), but when traps were separated over 9 m, no difference in catch rate was observed (Stamplecoskie et al., 2012). Therefore, lit traps may only catch more adult sea lamprey if other cues aggregate adult sea lamprey near the trap entrance first (Stamplecoskie et al., 2012).

Taste

Taste buds, the sensory end organs of the gustatory system, are located in the pharynx and water tube of the sea lamprey (Barreiro-Iglesias et al., 2010; Barreiro-Iglesias et al., 2008) compared to the oropharyngeal cavity, head, barbels, and gill arches of teleosts (Hansen et al., 2002; Finger, 1997; Puzdrowski, 1987), the ventral oral surface and gills bars in sharks and rays (Whitear and Moate, 1994), and the oral and the pharyngeal cavities in tetrapods (Stone et al., 1995). In mammals, the nasal, laryngeal and tracheal respiratory epithelium contains solitary chemosensory cells of the diffuse chemosensory system that function as sentinels against irritants and micro-organisms (Tizzano et al., 2010; Finger et al., 2003). Putative solitary chemosensory cells have been located in hagfish (Braun and Northcutt, 1998). Solitary chemosensory cells are associated with feeding in some teleosts (Finger, 1997; Kotrschal, 1996, 1995), where they are located in the skin, gills and pectoral fin rays of sea robins (*Prionotus carolinus*) and rocklings (genera *Ciliata* and *Gaidropsarus*) which utilize finger-like free rays to probe a substrate for food (Whitear and Kotrschal, 1988; Whitear, 1971). In the sea robin, the solitary chemosensory cells are innervated by spinal nerves located on the pectoral fin (Finger, 1982) and trigger feeding behaviour (Finger, 1997). In the sea lamprey, solitary chemosensory cells are on cutaneous papillae located around the oral cavity in all developmental stages and develop on the nostril, gill pores, and dorsal fin following metamorphosis (Suntres et al., 2020). Chemosensory stimuli for the gill papillae include bile acids, trout-derived chemicals, and amino acids (Daghfous et al., 2020; Baatrup and Døving, 1985).

Auditory system

The lamprey auditory system is less complex than gnathostomes but contains a macula communis with statolith and hair cells (Maklad et al., 2014). In lampreys, the macula communis is hypothesized to be where auditory responses are generated (Mickle et al., 2019). Juvenile and adult sea lamprey are sensitive to a narrow range of low frequency sounds ranging from 50 to 200 Hz (Mickle et al., 2019). This range is much narrower than teleosts which have Weberian ossicles and auditory bullae that can detect sounds ranging between 50 and 5000 Hz (Popper and Fay, 1999). In a laboratory microcosm, juvenile and adult sea lamprey exposed to low frequency sounds showed changes in behavior and often displayed increases in surface breeches and swimming (Mickle et al., 2019). Detection of low frequency sounds may be adaptive and allow sea lamprey to detect movements by stream-side predators, hydrodynamically challenging river reaches, or find mates that are moving rocks while constructing nests (Johnson et al., 2015a). Indeed, an instream study found that low frequency sound at 70 or 90 Hz caused avoidance in adult sea lamprey migrating upstream (Heath et al., 2021). More research is needed to understand how sound influences adult and juvenile migratory behavior in larger and hydrodynamically variable streams.

Electroreception

Lampreys are electroreceptive (Bodznick and Northcutt, 1981). Electroreception in lampreys is hypothesized to be homologous with other non-teleost fishes and amphibians (Ronan and Bodznick, 1991; Bodznick and Northcutt, 1981). Larval lampreys are electroreceptive 70 days post fertilization (Richardson and Wright, 2003) and microvillous cells in the epidermis of the branchial and tail regions seem to be where electrical cues are detected by larvae (Ronan, 1988). Adult lampreys detect electrical stimuli with epidermal end bud cells (Ronan and Bodznick, 1986). Electric fields are processed in dorsal medulla, the midbrain torus semicircularis, and optic tectum (Bodznick and Northcutt, 1981), with more recent work showing that the octovolateral system is associated with electroception (Chung-Davidson et al., 2004).

Lamprey electroreceptors are excited by cathodal fields and inhibited by anodal fields ranging from 1 to 10 μV/cm (Bodznick and Preston, 1983). Juvenile sea lamprey behaviorally respond to cathodal fields ranging from 0.1 to 30.0 μV/cm by increasing swimming activity, and if the field is anodal these behaviors are supressed (Chung-Davidson et al., 2004). In contrast, adult sea lamprey exposed to similar weak electric fields do not show behavioral responses and remain attached to the substrate. However, males, not females, exhibit increased lamprey GnRH-1 mRNA expression in the brain stem after exposure to electrical fields. This suggests that juvenile and adult sea lamprey can detect the fields, and that electrical cues may trigger endocrine responses in males that are associated with reproduction (Chung-Davidson et al., 2008).

Electrical field have been used to capture larval sea lamprey and block adult sea lamprey since nearly the inception of the control program in the Great Lakes (McLain et al., 1965). Electrofishing for larval lampreys has been optimized in both shallow and deep habitats (Steeves et al., 2003; Bergstedt and Genovese, 1994). Electrical barriers to block adult sea lamprey migrations have had mixed success at preventing sea lamprey recruitment (Tews et al., 2021; Johnson et al., 2021 - b), and all have blocked non-target fishes unless they are turned off or a fish bypass system is built around the electric field (Tews et al., 2021).

Future possibilities to exploit novel physiological features of sea lamprey for control

Metamorphosis

All lampreys undergo true metamorphosis, a process that relatively few other fishes undergo (Youson, 2003). Only two other groups of fishes include a true metamorphosis as part of their life history: the ~860 species in the actinopterygian subdivision Elopomorpha (tarpons, ten pounders, true eels) and all ~680 species in the order Pleuronectiformes (flatfishes) of the subdivision Euteleostei (Manzon et al., 2015; Dufour et al., 2012; Youson, 1988). In sea lamprey, metamorphosis from the filter-feeding larval stage into the parasitic juvenile stage is a major life history event and, as early as 1980, metamorphosis was identified as a potential life stage to target for additional sea lamprey control tools (Lamsa et al., 1980). Intensive investigation has revealed that metamorphosis in sea lamprey is controlled by several environmental and biological factors (Youson, 2003; Kao et al., 1997; Holmes and Youson, 1994; Potter, 1980; Purvis, 1980; Lowe et al., 1973). The key environmental trigger appears to be the rise in water temperature in the late spring/early summer, and peak rates of metamorphosis are observed at ~21 °C in controlled conditions (Youson, 2003; Holmes and Youson, 1998; Holmes and Youson, 1994; Purvis, 1980). Larvae will delay metamorphosis if they are not of sufficient size (length and weight) or are lacking in body lipid stores, presumably to ensure survival during this prolonged non-tropic stage (Potter, 1980; Youson, 1980; O'Boyle and Beamish, 1977; Lowe et al., 1973). Lamprey undergoing spontaneous metamorphosis show sharp declines in the levels of T_3 (triiodothyronine) and T_4 (thyroxine), which increase over time in larvae, a pattern that is unique amongst metamorphosing vertebrates (Lintlop and Youson, 1983; Wright and Youson, 1977). Better understanding of the multimodal factors that trigger metamorphosis could enable more precise and efficient treatment protocols.

Early initiation of the non-trophic metamorphic stage could lead to increased mortality due to starvation, reducing the population of parasitic juveniles and eventually spawning adults. For example, treatment with the goitrogen potassium perchlorate ($KClO_4$), an anionic competitor of iodide uptake that inhibits the synthesis of thyroid hormones, initiates metamorphosis in 100% of treated larvae under certain conditions (e.g., warm water) (Manzon and Youson, 1999). Treatment with exogenous thyroid hormone blocks $KClO_4$-induced metamorphosis by countering the reduction in thyroid hormone synthesis induced by treatment with the goitrogen, further demonstrating the close link between thyroid signals and metamorphosis (Manzon et al., 1998). However, more work is needed in this area, as a decline in serum T_3 and T_4 is necessary but alone not sufficient to induce metamorphosis, as animals acclimated at 18 °C, but not 3 °C, show potassium perchlorate-induced metamorphosis (Manzon and Youson, 1999). Nevertheless, manipulation of the timing of metamorphosis via the environmental and biological factors described above or by others (Youson, 2003) could foreseeably delay or even prevent metamorphosis. The highly specific nature of metamorphosis, which is absent in virtually all other fishes in the Great Lakes region, may enable the development of control techniques with little or no off-target effects.

Feeding and digestion

The buccal gland secretion, lamphredin, is an essential adaptation that facilitates blood ingestion by sea lamprey (Xiao et al., 2012; Gage and Gage-Day, 1927). With the recent publication of a lamphredin proteome (Li et al., 2018a), as well as the sea lamprey somatic and germline genomes (Smith et al., 2018; Smith et al., 2013), it may soon be possible to use genetic technologies (e.g., CRISPR-cas9; RNA interference) to target genes involved in producing key components of lamphredin (Thresher et al., 2019; York et al., 2021). For example, reduction in the analgesic properties of lamphredin may promote host attempts to dislodge attached lamprey. Reduction in the anti-coagulant properties of lamphredin may make it more difficult for sea lamprey to feed and reduce blood ingestion, forcing them to abandon hosts by preventing the ingestion of sufficient blood needed for growth or survival. Such an approach could be particularly useful in much smaller, newly metamorphosed sea lamprey in which lipid stores are depleted following metamorphosis (O'Boyle and Beamish, 1977), thereby increasing their vulnerability to predation and starvation.

Interference with appetite digestive processes in either larval or juvenile stages could also be targeted using genetic technologies. For instance, if nutrient ingestion were impaired in larval sea lamprey, there would be insufficient accumulation of lipid stores, which are critical for allowing the animals to enter and complete the non-trophic period of metamorphosis (Manzon et al., 2015; Youson, 2003). For example, impairing mucus secretion by larval endostyle would impair the larva's ability to captures food particles, leading to a prolonged larval stage (which could aid in the scheduling of treatments) or even starvation.

Similarly, lipid accumulation by parasitic juveniles is necessary to fuel upstream migration, maturation, and spawning during the adult upstream migration phase (Kao et al., 1997; Beamish et al., 1979; O'Boyle and Beamish, 1977). Impairment of the juvenile's capacity to pursue and attach to potential hosts, suppress their appetite, or inhibit digestion could lead to insufficient lipid accumulation and starvation during the spawning migration. Again, the use of genetic technologies that inhibit or knockout the genes involved in the stimulation of appetite, food acquisition, the production of proteolytic digestive enzymes, or nutrient uptake may represent viable options for sea lamprey control.

Reproduction

Disruption of sea lamprey reproduction in the Great Lakes region could offer a highly species-specific way of controlling this invasive pest (Christie and Goddard, 2003; Docker et al., 2003; Li et al., 2003; Sower, 2003). Detailed reviews of lamprey sex differentiation, sex determination, reproductive endocrinology (e.g., hypothalamic-pituitary axis and sex steroids), and sexual maturation are provided elsewhere (Docker et al., 2019; Sower, 2015). Here, we highlight some aspects of lamprey reproduction that distinguish them from the jawed fishes. How these differences could potentially be exploited to provide opportunities for more targeted control are not always clear, but it is clear that lamprey reproduction differs from that of other vertebrates in a great many ways.

Gonadal development and anatomy of the reproductive system

Lampreys possess a single elongated gonad which remains histologically undifferentiated for several years (Docker et al., 2019; Hardisty, 1971). This delay in gonadogenesis, which is unusual in fishes, is presumably the result of the extremely prolonged larval stage (Evans et al., 2018; Beullens et al., 1997a; Beullens et al., 1997b). Ovarian differentiation occurs during the larval stage, but testicular differentiation does not occur until metamorphosis. Lampreys are sometimes said to pass through an initial female or intersexual stage, because oocytes appear to develop in most larvae regardless of future sex, but oocyte growth is more synchronized and extensive in female larvae. In future males, germ cells remain undifferentiated throughout the larval stage (Docker et al., 2019; Hardisty, 1971). Furthermore, although it has typically been thought that sex is fixed once ovarian differentiation is complete, studies using gonadal biopsy methods showed that sex reversal appears possible as long as undifferentiated germ cells remain in the gonads (Barker and Beamish, 2000; Lowartz and Beamish, 2000). These results suggest that the lamprey gonad might remain labile (i.e., capable of being influenced by environmental, hormonal, or genomic manipulation) throughout the larval stage (William et al., 2002).

After metamorphosis, parasitic lampreys remain sexually immature during the feeding stage. Vitellogenesis does not occur until near the end of parasitic feeding and proceeds during upstream migration (Docker et al., 2019; Hardisty, 1971). As in other vertebrates, vitellogenin synthesis is induced in the liver by estrogens, and these precursors of the major egg yolk proteins are delivered via the bloodstream to the growing oocyte. In male lampreys, spermatogenesis occurs in cysts, as it does in other non-amniote vertebrates (i.e., in fishes and amphibians), although spermatogenesis in amniotes (reptiles, birds, and mammals) occurs in seminiferous tubules (Yoshida, 2016). Lampreys lack Sertoli cells, the somatic cells in the testes of jawed vertebrates that help in the production and nourishment of developing sperm (Yoshida, 2016; Schulz et al., 2010), although similar functions appear to be performed in lampreys by lobule cells (Hardisty, 1971).

Like teleost fishes, lampreys (and hagfishes) lack the Müllerian ducts that develop into the female reproductive organs (including oviducts) (Adolfi et al., 2019). However, while teleosts secondarily lost their Müllerian ducts, lampreys and hagfishes never had them (Adolfi et al., 2019). This is relevant because genes encoding the anti-Müllerian hormone and the anti-Müllerian hormone receptor 2 genes are retained as genes associated with sex differentiation in teleosts, but homologs of these genes have not been found in lampreys (see below). Likewise, vasa efferentia are absent in male lampreys. During spawning, the gametes are released into the body cavity and then to the exterior through the pore on the urogenital papilla (Applegate, 1950).

Sex determination

Potential manipulation of sea lamprey sex ratio, contingent upon the development of effective and reliable techniques for doing so, has major potential implications to the sea lamprey control program in the Great Lakes, although the genetic and/or environmental factors that influence sex determination and sex ratios in lampreys continue to elude biologists (Docker et al., 2019; McCauley et al., 2015). Male-biased sex ratios under conditions of high population density or slow growth have led to suggestions of environmental sex determination (ESD; Johnson et al., 2017; Docker and Beamish, 1994; Torblaa and Westman, 1980), but evidence for ESD in lampreys is equivocal (Docker and Hume, 2019). Furthermore, no fish species with exclusively ESD are known. Instead, ESD and genotypic sex determination (GSD) have been shown to co-exist in several fish species (Palaiokostas et al., 2015; Yamamoto et al., 2014), with environmental conditions influencing a predominantly GSD mechanism rather than ESD operating alone (Ospina-Alvarez and Piferrer, 2008).

Identifying the genetic basis of sex determination in sea lamprey would establish the foundation for future genetic control. Although sex determination mechanisms are poorly known in most fishes, they can be highly variable even among closely related species (Cutting et al., 2013; Siegfried, 2010), suggesting that a genetic basis for sex determination in lampreys, if one exists, could be different from that of any other species. Sex determining genes are a particularly good target for eradicating invasive species by allowing one sex to be bred out of the population, resulting in population collapse (Backus and Gross, 2016; Champer et al., 2016). For example, a CRISPR-Cas9 sex-ratio distortion system that produces highly male-biased offspring has been developed in the malaria mosquito vector *Anopheles gambiae* (Galizi et al., 2016). Several schemes for control by manipulation of sex chromosomes exist (Schill et al., 2016; Thresher et al., 2014; Cotton and Wedekind, 2007; Gutierrez and Teem, 2006), but at this time, their potential for use in invasive sea lamprey is limited as we do not yet know the sex determination mechanism employed by lampreys, and hormonal sex control or sex reversal has not been achieved in lampreys (Docker, 1993; Hardisty, 1965).

Genetic basis of sex differentiation and sexual development

Unlike the master sex-determining gene that activates the developmental cascade leading to the development on an ovary or testis, many of the genes involved in the downstream sex differentiation process are conserved among fishes (Cutting et al., 2013; Siegfried, 2010). However, given the long period of divergence between lampreys and other vertebrates, some genetic differences might be expected; in fact, some genes implicated in sex differentiation in other vertebrates are not evident at all in lampreys. For example, genes encoding the anti-Müllerian hormone and the anti-Müllerian hormone receptor 2 genes (*amh* and *amhr2*, respectively) appear to have male-specific effects in many jawed vertebrates (Josso et al., 2001) and are retained as genes associated with male differentiation in teleosts (Ijiri et al., 2008; Moringa et al., 2007), even though teleosts have secondarily lost their Müllerian ducts. However, homologs of *amh* and *amhr2* have not been found in lampreys (Adolfi et al., 2019).

Nevertheless, there is evidence that at least some of the same genes involved in ovarian and testicular development in other vertebrates play similar roles lamprey sex differentiation (Mawaribuchi et al., 2017; Spice et al., 2014). For example, Mawaribuchi et al. (2017) examined *DMRT1* expression patterns in larval and post-metamorphic Far Eastern brook lamprey (*Lethenteron reissneri*), and found that *DMRT1* expression, which is required for male development in birds and at least one species of flatfish (Chen et al., 2014; Shetty et al., 2002; Smith et al., 1999), was significantly greater in post-metamorphic testes than in ovaries (Mawaribuchi et al., 2017). One of the key steroidogenic enzyme genes involved in ovarian differentiation appears to be aromatase *CYP19a1*. CYP19A1 converts androgens to estrogens, and it appears to be essential for ovarian differentiation in virtually all vertebrate species examined (Tao et al., 2013; Piferrer and Guiguen, 2008; Vizziano et al., 2007; D'Cotta et al., 2001; Nakamura et al., 1998). CYP19 activity has been found in lampreys (Callard et al., 1980), and a partial *cyp19* gene sequence has been identified in sea lamprey transcriptomic data (Tamanna Yasmin, University of Manitoba, pers. comm., July 2020). Even if these are not the "master" sex-determining genes, editing of key genes involved in the sex differentiation process or subsequent gonadal development nevertheless holds promise for genetic control methods that could distort sex ratio or impair reproductive function in a highly species-specific manner (see Ferreira-Martins et al., 2021; York et al., 2021).

Reproductive endocrinology

The hypothalamic-pituitary system in lampreys is generally considered to be less derived than that of other vertebrates, representing an evolutionarily intermediate stage of hypothalamic-pituitary development consisting of overlapping hypothalamic-pi tuitary–gonadal (HPG) and hypothalamic-pituitary-thyroid (HPT) axes (Sower, 2018, 2015; Sower et al., 2009). Not surprisingly, given their long divergence from all other vertebrates, some of the hormones that coordinate the axis and regulate reproductive physiology are different in lampreys and these differences could be exploited in a variety of ways for sea lamprey control (Docker et al., 2003; Sower, 2003). For example, three unique gonadotropin-releasing hormones (GnRHs) have been characterized, and they have potential for species-specific sterilization of male and female sea lamprey. Unlike the chemosterilant bisazir, which is equally hazardous to humans, sea lamprey-specific GnRH analogs would likely be non-toxic to non-target organisms and could potentially even be administered streamside (Docker et al., 2003; Sower, 2003).

Similarly, lampreys appear to use a mix of classical and non-classical reproductive steroids, including steroids that are different from those of other vertebrates in that they possess an additional hydroxyl group at the C15 position b (Docker et al., 2015; Bryan et al., 2008). It is possible that these 15-hydroxylated steroids evolved as functional hormones in parasitic lampreys so that lampreys would be less susceptible to the influence of the reproductive hormones in its host's blood. Alternatively, these 15-hydroxylated steroids may simply represent an ancestral form of steroid hormone. Many of the gonadal steroids thought to act as hormones in lampreys still have not had functions clearly defined, but decades of study have provided insights into steroid synthesis in lampreys, and sex- and stage-specific differences in plasma concentrations have been used to infer the functional role of different steroids. For example, due to changes in progesterone (P) with stage of maturity and in response to GnRH, Sower (1990) suggested that P is a functional hormone in lampreys (Sower, 1990). More recent studies examining 15α-P levels in lampreys show that they increase even more dramatically in response to GnRH injections or pituitary extracts (Young et al., 2007; Bryan et al., 2004), and 15α-P is also the only steroid that appears to respond to GnRH or pituitary extract in a dose-dependent fashion (Young et al., 2007). 15α-testosterone (15α-T) has been identified at low concentrations in lamprey plasma, and levels vary with sex and stage (Mesa et al., 2010; Bryan et al., 2003) and in response to hypothalamic and pituitary hormones (Young et al., 2004a; Young et al., 2004b). There is also strong evidence that estradiol (E_2) is a functional hormone in lampreys, but its role is somewhat enigmatic. As in other vertebrates, plasma E_2 levels have been associated with vitellogenesis in females (Mewes et al., 2002). However, E_2 levels are often higher in males than in females, and it appears to play a major role in the reproductive physiology of male lampreys (Bryan et al., 2008). 15α-E_2 is present in the plasma at lower levels than E_2, and the levels do not change after injection of GnRH, suggesting that it is likely not a hormone in lampreys (Docker et al., 2019). Although there is clearly still much to be learned about the gonadal steroid hormones in lampreys, developing lamprey-specific analogs that could be used to control invasive sea lamprey while minimizing non-target effects holds promise.

Exploiting features of lamprey physiology for conservation

Swim performance and energetics

Many anadromous lampreys are incapable of sustaining the swim speeds needed to pass even very low-elevation barriers (Bice et al., 2019; Silva et al., 2019; Foulds and Lucas, 2013; Jackson and Moser, 2012). Novel features of their swimming and/or climbing performance have been exploited to aid native lamprey passage at both small- and large-scale barriers (Moser et al., 2015a). Lamprey-specific fishways that rely on climbing behavior of Pacific lamprey have been developed (Frick et al., 2017; Moser et al., 2011), and this technology is currently being explored for pouched lamprey (*Geotria australis*) in New Zealand (C. Baker, NIWA, pers. comm., Sept. 2020). In addition, use of velocity disruptors to reduce near-bottom flows have been developed for Pacific lamprey (Moser et al., 2019), and studded tiles have been added at low elevation weirs to aid native sea lamprey and European river lamprey passage (Tummers et al., 2018).

Interestingly, there is some evidence that swimming performance or motivation of adult Pacific lamprey is reduced as they near reproductive readiness (Moser et al., 2021; Hanchett, 2020; Kirk et al., 2016). A more thorough understanding of this relationship could be used to target aids to passage for long distance migrants like Pacific lamprey, pouched lamprey, and sea lamprey in their native range. Aids to passage may need to require even less exertion on the part of adult lampreys as they near spawning grounds and the time of reproduction. In addition, evidence that anadromous lampreys experience fatigue when faced with multiple, energetically-costly obstacles (Hanchett, 2020; Kirk et al., 2016; Kemp et al., 2009) could help in development and placement of velocity refuges or resting pools (Moser et al., 2021).

A better understanding of the swim performance of outmigrating juveniles is needed to protect them at dam bypasses, water abstraction points, and other threats to passage (Moser et al., 2015b). Juvenile lampreys are able to pass through dam turbines with less injury than bony fishes of similar size, largely due to their lack of a swim bladder and resulting tolerance of pressure changes (Colotelo et al., 2012). However, their small size and anguilliform body plan make them susceptible to injury at pump intake screens, hydropower turbine strainers, juvenile salmonid bypass screens, and raceway tail screens at hatcheries and salmonid holding areas (Moser et al., 2015b).

Most recently with the planned construction of facilities such as FishPass (Zielinski et al., 2020), there's growing interest in control systems that exploit multiple traits (e.g., velocity barriers, seasonal barriers, baited traps) for improved efficiency of control. This multi-trait approach has the potential to mitigate the weakness

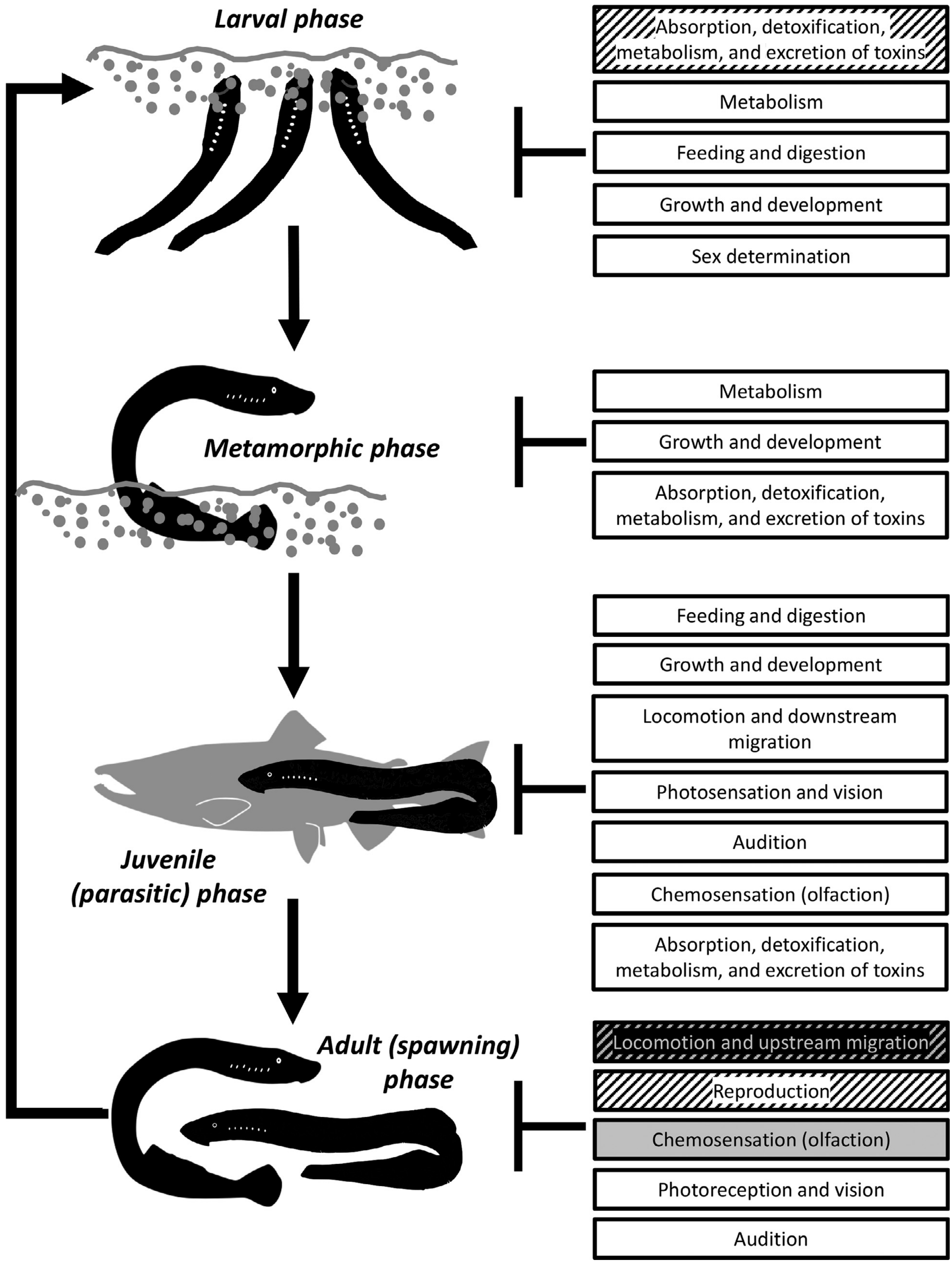

Fig. 3. Features of lampreys relevant to control and conservation, divided into current or field-tested methods (black), methods currently under investigation (gray), and proposed or potential methods (white). Methods of control either target the indicated life stage directly (e.g., lampricides) or prevent that life stages from being successful (e.g., traps and barriers that prevent mature lamprey from entering the spawning stage). Features that fit into multiple categories are identified with hatched boxes representing each category.

inherent in single trait-based control techniques similar to the "Swiss cheese model" of accident causation (Reason et al., 1990).

Olfaction and chemical cues

Because most lamprey species use chemical cues emitted from conspecifics to coordinate spawning migration and mating (Buchinger et al., 2019; Johnson et al., 2014b; Fine et al., 2004), similar olfactory-based tactics as those proposed for sea lamprey control in the Great Lakes (Fissette et al., 2021) may also be used in reverse to benefit lamprey restoration. One possible tactic is to use larval odors to attract migratory lampreys into the best available watersheds. The simplest way to create larval chemosensory attractants may be translocation of larval lampreys or translocation of adult lampreys prior to spawning (Ward et al., 2012). Doing so does not require identification, synthesis, and application of the chemical cue, and the process of translocating "jump starts" the restoration process. Another possible tactic is to use alarm cues to keep migratory lampreys from entering watersheds with ecological traps such as dams, water withdrawals, or high numbers of predators (Arakawa and Lampman, 2020; Schultz et al., 2017). On a smaller spatial scale, alarm cues and attractive conspecific cues may be useful at dams to direct lampreys away from turbines and toward fishways. As in the Great Lakes, assessment of lamprey-specific chemical cues released by larvae or adults (Buchinger et al., 2015; Johnson et al., 2014b) may complement on-going assessment with electrofishing and environmental DNA (Docker and Hume, 2019).

Reproduction and metamorphosis

As noted above, substantial advances have been made in our understanding of sea lamprey reproduction in the last 2–3 decades, but our knowledge of the reproductive biology of native lamprey species is more limited. Nevertheless, much of what has been learned about sea lamprey reproduction likely applies to other lamprey species and could be used to develop conservation strategies. For instance, successful rehabilitation or conservation of at-risk lamprey species would be greatly enhanced through the development of methods to rear the animals in hatcheries. Indeed, such strategies have led to significant advances in ongoing efforts to rejuvenate and sustain Pacific lamprey populations in the US northwest (Barron et al., 2016; Moser et al., 2015a) and river lamprey in Europe (Kujawa et al., 2018), though others have emphasized the need for caution in using this approach (Hilborn, 1992).

Key to the development of lamprey aquaculture for conservation is ensuring that the stocked larvae undergo metamorphosis. It is well established that the incidence and timing of metamorphosis in sea lamprey depends upon both biotic factors including population density, body size, lipid reserves and endocrine status, as well as abiotic factors such as temperature and nutrient availability (Johnson et al., 2017; Manzon et al., 2015). Data gaps include learning more about the role that body size and lipid reserves play in the initiation of metamorphosis, and how the patterns of endocrine regulation resemble those observed in sea lamprey. Recent studies on sea lamprey have suggested that sea lamprey living in less productive waters undergo metamorphosis later and at smaller body sizes than those in more eutrophic systems (Johnson et al., 2017; Johnson et al., 2016; Johnson et al., 2014a). Thus, the effects of water quality on the growth, timing, and incidence of metamorphosis in native lampreys will be key to any efforts to conserve or replenish populations.

Summary and conclusions

The sea lamprey's status as an invasive species in the Great Lakes of North America has generated considerable interest in the development of specific and effective methods of population management. Most methods of sea lamprey control that have been tested in the field – lampricides, traps and barriers, sterile male release, and pheromones – exploit some aspect of the sea lamprey's underlying physiology (Fig. 3 – black boxes). The future of sea lamprey control stands to benefit from further exploitation of the lamprey's biological, evolutionary, ecological, and physiological traits. A more thorough understanding of these traits could aid in the development of more effective strategies of sea lamprey control, but could also help protect and rehabilitate native lamprey populations, which continue to be threatened by habitat degradation due to anthropogenic activities such as dredging of depositional habitat, barriers to migration, overharvest, and climate change (Maitland et al., 2015).

There are many processes unique to lampreys that could be potentially exploitedfor improved sea lamprey control (Fig. 3 - white boxes). For instance, the sea lamprey's much lower capacity to detoxify and excrete phenolic compounds is used to control their populations in the Great Lakes with TFM to more-or-less specifically target larval sea lamprey in their natal streams. However, by conducting additional studies on the absorption, distribution, metabolism, and excretion (ADME) of other chemicals by these animals, it may be possible to identify other compounds that specifically target sea lamprey in not only the larval stage, but during metamorphosis or even the parasitic phase. Similarly, interventions that interfere with larval sea lamprey metabolism, or growth and development, could lower their ability to enter and successfully complete metamorphosis. Manipulating the sex ratio of lamprey could also be a powerful method of sea lamprey control, but this is contingent on better characterizing the underlying environmental or genetic factors of sex determination. Impairing the sea lamprey's ability to feed, particularly in the parasitic phase, could compromise their growth and development to prevent them reaching the mature adult stage and reproducing. Understanding and exploiting unique aspects of lamprey locomotion have already been used in the form of barriers and traps to reduce or prevent adult sea lamprey from spawning. However, better knowledge of these unique aspects of lamprey swim performance and migration could lead to improved barrier and trap design, for not only adults migrating upstream, but possibly for juveniles migrating downstream, which could be augmented by altering their movements and behaviour through a better understanding of sensory processes including vision and photoreception, olfaction, and hearing.

The major advantage of targeting novel features of sea lamprey physiology is that it provides increased specificity and reduced effects on non-target invertebrates and teleosts. While these features might provide inviting targets for sea lamprey control, many of them are likely also characteristics of other lampreys, which could undermine efforts to conserve native species whose populations overlap with those of invasive sea lamprey. Hence, it will be necessary to balance the needs of sea lamprey control with those of native lamprey conservation by learning more about the vulnerabilities of both sea lamprey and native lampreys in these areas. To achieve such balance, it will be critical to use comparative physiology approaches with modern molecular tools to better characterize the similarities, differences and vulnerabilities among lamprey species.

In the last 50 years, new discoveries have revolutionized how science in all disciplines is conducted, communicated, and implemented to solve ecological challenges including those posed by invasive species and anthropogenic disturbances. Incorporating new or emerging techniques, such as "omics" and gene editing tools, along with thoughtful application of more established physiological approaches (e.g., biochemical assays, respirometry), will further improve our fundamental knowledge of the environmental, metabolic, locomotory, sensory, behavioural and reproductive strategies that have allowed lampreys in their present form to thrive for hundreds of millions of years. Such knowledge will also allow us to better predict and mitigate anthropogenic threats to the survival of vulnerable native lamprey populations, and to refine, improve and develop better methods to control invasive sea lamprey populations. As the present review illustrates, this will require a combination of approaches from different disciplines and sub-disciplines, ranging from molecular biology to biochemistry to whole animal physiology and population ecology, not to mention chemistry and engineering. Such an approach will ultimately open doors of inquiry that lead to more and diverse methods of sea lamprey control and native lamprey conservation in not only the Great Lakes, but other parts of the world where native lampreys are under threat.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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