The emerging role of pharmacology in understanding consumer–prey interactions in marine and freshwater systems

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Synopsis Within our lakes, streams, estuaries, and oceans, there is an astounding chemodiversity of secondary metabolites produced by microbes, algae, and invertebrates. Nearly 30 years of study have yielded hundreds of examples in which secondary metabolites alter the foraging behavior or fitness of aquatic consumers, or both. However, our understanding of the mechanisms that mediate the fate and consequences of these metabolites in aquatic consumers remains in its infancy. Interactions between metabolites and consumers at the molecular and biochemical level are the purview of modern pharmacology, which is rooted in the long history of human–drug interactions and can be adopted for ecological studies. Here, we argue that a pharmacological approach to consumer–prey interactions will be as productive within aquatic systems as it has been for understanding terrestrial systems. We review the diversity of secondary metabolites in aquatic organisms, their known effects on the feeding behaviors and performance of aquatic consumers, and the few studies that have attempted to describe their biochemical manipulation within consumer tissues, i.e., their absorption, distribution, metabolism (including detoxification), and excretion. We then highlight vexing issues in the ecology and evolution of aquatic consumer–prey interactions that would benefit from a pharmacological approach, including specialist-versus-generalist feeding strategies, dietary mixing, nutrient–toxin interactions, and taste. Finally, we argue that a pharmacological approach could help to predict how consumer–prey interactions are altered by global changes in pH, water temperature and ultraviolet radiation, or by pollution. Arguably, the state of knowledge of aquatic consumer–prey interactions is equivalent to that faced by ecologists studying terrestrial herbivores in the 1970s; the literature documents profound variation among consumers in their feeding tolerances for secondary metabolites without a thorough understanding of the mechanisms that underlie that variation. The subsequent advancement in our understanding of terrestrial herbivores in the intervening decades provides confidence that applying a pharmacological approach to aquatic consumers will prove equally productive.

Introduction

Terrestrial vascular plants are fantastic chemists (Fraenkel 1959; Rosenthal and Berenbaum 1991), yet produce only a fraction of the chemodiversity found on earth. This is because the absolute number of land-dwelling plants is dwarfed by the microbial, algal, and invertebrate biodiversity living in freshwater and marine habitats, many of which are prolific chemists (Wolfe 2000; Harper et al. 2001; Paul and Puglisi 2004; Leflaive and Ten-Hage 2007; Blunt et al. 2008; Camacho 2008). Aquatic chemodiversity has been the focus of natural-product chemists for decades, motivated by the potential of aquatic organisms to produce human pharmaceuticals (Bhadury and Wright 2004; Dunlap et al. 2007; Berry et al. 2008). In parallel with this effort to discover drugs, ecologists studying aquatic systems have simultaneously gathered overwhelming evidence that many potential drugs can play important ecological roles, have no known

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primary metabolic function, and thus should be considered secondary metabolites (SM) (Fraenkel 1959).

While the ecological roles of SMs are numerous, one principal effect is the deterrence or poisoning of co-occurring consumers (Hay 1996; Paul et al. 2001; Hay and Kubanek 2002), including herbivores (those principally feeding on plants and algae), carnivores (those principally feeding on invertebrates), and omnivores (those feeding on both). The evolution of aquatic chemical defenses against consumers is not surprising, given the profound impacts that consumers have on prey populations and the long history of their associations in the seas (10s to 100s of millions of years) (Vermeij 1994; Vermeij and Lindberg 2000; Knoll 2003). However, despite decades of research on the chemical mediation of aquatic consumer–prey interactions, there remain large gaps in our understanding. Most frustratingly, consumers' responses to SMs are bewilderingly variable (Hay and Fenical 1988; Paul 1992a). Arguably, this complexity in consumers' responses has historically led ecologists to focus primarily on the chemical defenses of prey and to neglect mechanisms underlying their responses, a bias that is not unique to aquatic systems (Karban and Agrawal 2002; Sotka and Whalen 2008).

The effectiveness of a given SM as a feeding deterrent or as a toxin is not an inherent trait of the compound, but rather reflects biochemical interactions between that metabolite and a particular consumer (Paul 1992a). Interactions between metabolites and consumers at the molecular and biochemical levels are the purview of modern pharmacology, which is rooted in the long history of human–drug interactions and can be adopted for ecological studies (Fig. 1; McLean and Duncan 2006; Sorensen and Dearing 2006). In general, pharmacologists define the mechanisms by which animals process SMs and other xenobiotics by four major parameters: absorption, distribution, metabolism (i.e., detoxification), and excretion (collectively abbreviated as ADME) (Gibaldi and Perrier 1982; Neubig 1990; Hayes 2001; Klaasen and Watkins 2003). The ADME of an SM is influenced by the activity of efflux transporters that regulate absorption, distribution, and excretion (termed phase III enzymes), as well as oxidative and conjugative enzymes that control xenobiotic metabolism (termed phase I and II enzymes, respectively). The interactions between a parent xenobiotic, its initial metabolites, and ADME enzymes will collectively influence the effective concentration that, in turn, influences consumers' responses (Fig. 1).

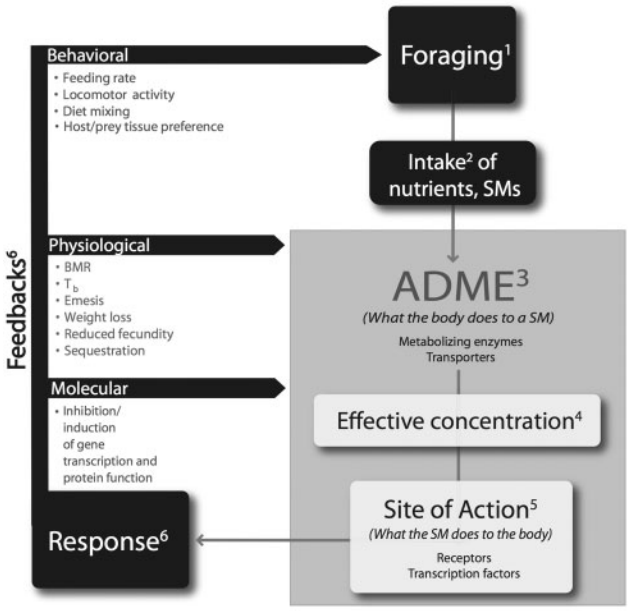

Fig. 1 A pharm-ecological approach to consumer–prey interactions. The gray shaded box highlights the purview of pharmacology, which addresses the physiological mechanisms that determine the concentration and fate of ingested secondary metabolites (SMs). Processes that are outside of the gray shaded box (especially foraging behavior and consumer response) typify most studies in aquatic chemical ecology. The foraging behavior of consumers (1) attempts to maximize intake of nutrients and minimize exposure to SMs (2). Ingested SMs are absorbed, distributed, metabolized (i.e. detoxified), excreted (ADME), or undergo a subset of these processes (3). ADME determines the effective concentration (4) of SMs at target proteins and DNA (a process termed pharmacokinetics). This effective concentration then effects changes in consumers' tissues [a process termed pharmacodynamics (5)]. The interactions of SMs with consumer tissues will affect responses via molecular, physiological, and behavioral feedback mechanisms (6). This figure extends ideas represented by McLean and Duncan (2006) and Sorensen et al. (2006).

ADME mechanisms are poorly described for all, but a handful of aquatic consumers and this lack of knowledge impedes our ability to explain variance in feeding responses among individuals, populations, and species (Paul et al. 2001; Targett and Arnold 2001; Sotka and Whalen 2008). Here, we argue that a pharmacological approach to consumer–prey interactions will be as productive within aquatic systems as it has been for understanding terrestrial herbivores (Yu 1996; Feyereisen 1999; Berenbaum 2002; Dearing et al. 2005; Sorensen and Dearing 2006; Després et al. 2007; Li et al. 2007). First, we review the diversity of SMs produced across a broad swath of aquatic biodiversity and highlight studies that examine the impact of SMs

on consumers, the consumers' ADME mechanisms, or both. Second, we highlight some vexing issues in the ecology and evolution of consumer–prey interactions that would benefit from a pharmacological approach, including the evolution of specialization, dietary mixing, nutritional–toxin interactions, the evolution of taste, and the potential for global climatic change and contamination of aquatic habitats to alter the chemical mediation of marine biotic interactions.

Although it is clear that the integration of pharmacology and ecology, termed Pharm-Ecology (Forbey and Foley, this issue), is in its infancy, our hope is that this review will invigorate the pursuit of ADME studies of aquatic consumers. Arguably, the state of knowledge of aquatic consumer–prey interactions is equivalent to that faced by ecologists studying terrestrial herbivores in the 1970s; the literature documents profound variation among consumers in their feeding tolerances for secondary metabolites without a thorough understanding of the mechanisms that underlie that variation. The subsequent advancement in our understanding of terrestrial herbivores in the intervening decades provides confidence that applying a pharmacological approach to aquatic consumers will prove equally productive.

Chemical defenses of aquatic prey and the response by consumers

Although some metabolites are unique to either marine or terrestrial habitats (Hay and Fenical 1988), a review of the most recent edition of the Dictionary of Marine Natural Products (Blunt and Munro 2008) reveals that the diversity of broad structural classes (e.g. terpenes, alkaloids) is as impressive for aquatic groups as it is for vascular plants (Harborne 1988; Wink 2003; Table 1). One must exercise caution in assessing these patterns because of publication bias. For instance, the true chemodiversity of natural products is likely far greater than that represented here, as many marine organisms have yet to be examined (Harper et al. 2001). Moreover, in recent years, the discovery of natural products has been biased toward microalgae and cyanobacteria, which account for 50% of new compounds since 2000 (Maschek and Baker 2008). Despite these inherent biases, it is clear that aquatic consumers regularly encounter prey that produce SMs.

Below, for each major kind of aquatic prey, we highlight its chemodiversity and outline studies that have described the deterrent effects of SMs on feeding, the post-ingestive effects of SMs, and the ADME mechanisms that mediate both processes. We largely focus this review on consumers' interactions with lipophilic SMs rather than with water-soluble SMs (e.g. phlorotannins; Targett and Arnold 2001; Honkanen and Jormalainen 2008) because lipophilic compounds are more readily absorbed within consumer tissues and are more likely to be toxic.

Macroalgae

The structural diversity, taxonomic distribution and biosynthetic pathways of macroalgal SMs are well studied and have been the subject of several extensive reviews (Hay and Fenical 1988; Paul 1992a; Harper et al. 2001; Amsler and Fairhead 2006; Maschek and Baker 2008). Macroalgae produce many of the same chemical classes found in higher plants, including terpenes, acetogenins, alkaloids, and polyphenolics (Table 1). More than half of the described metabolites are terpenes and their derivatives. With the exception of water-soluble phlorotannins and coumarins, most of the effective SMs from macroalgae are lipid-soluble and occur in concentrations of less than approximately 2% dry mass.

A large body of research now exists that documents the important role of these metabolites in mediating algal–herbivore interactions (reviewed by Hay and Fenical 1988; Hay 1992; Hay and Steinberg 1992; Paul 1992a; Hay 1996; Paul et al. 2001; Van Alstyne et al. 2001; Amsler et al. 2008; Jormalainen and Honkanen 2008; Pereira and da Gama 2008). Virtually all of this work focuses on the ability of macroalgal SMs to deter feeding by a phylogenetically-diverse suite of herbivores, including fishes, urchins, crustaceans, and molluscs.

One of the earliest patterns to emerge from these feeding-preference studies, much to the dismay of biologists (Hay 1992; Hay and Steinberg 1992; Paul 1992a) but perhaps not a surprise to pharmacologists, was the tremendous variation among consumers' responses. As an example, we have summarized a series of feeding assays (Supplementary Table 1) with five diterpene alcohols (termed dictyols) produced from two species of the brown seaweed *Dictyota*. The backbones of the dictyols are similar and structural differences arise with the placement of acetate, hydrogen, or hydroxyl groups. As has been pointed out within several systems (see reviews by Hay 1996; Paul et al. 2001; Stachowicz 2001; Targett and Arnold 2001), a single macroalgal metabolite (e.g., E) can either deter or attract, or induce no behavioral effect among co-occurring

Table 1 Biological distribution of putative secondary metabolites

Structural Classes	Bacteria[a] (%)	Dinoflagellates and other Phytoplankton (%)	Chlorophyta, Rhodophyta and Phaeophyta (%)	Invertebrates[b] (%)	Vascular Plants (%)
Peptides	267 (22)	12 (4)	39 (2)	832 (8)	
Alkaloids	578 (48)	73 (23)	165 (6)	2993 (30)	12,000 (34)
Cyanogenic glycosides					60 (<1)
Glucosinolates					100 (<1)
Terpenes					
Monterpenes	1 (<1)		194 (8)	48 (<1)	2500 (7)
Sesquiterpenes	8 (1)	11 (3)	391 (15)	900 (9)	5000 (14)
Diterpenes	7 (1)	2 (1)	524 (21)	2244 (23)	2500 (7)
Sesterterpenoids	1 (<1)	11 (3)		604 (6)	
Triterpenoid	78 (7)	22 (7)	162 (6)	552 (6)	5000 (14)[c]
Meroterpenoids	16 (1)	1 (<1)	211 (8)	435 (4)	
Tetraterpenoids					500 (1)
Prenylated quinones and hydroquinones		1 (<1)	4 (<1)	17 (<1)	800 (2)
Polyketides					
Acetogenins			152 (6)	31 (<1)	
Polyethers	7 (1)	77 (24)	20 (1)	87 (1)	
Other	136 (11)	84 (27)	202 (8)	489 (5)	750 (2)[d]
Simple aromatic products					
Phlorotannins			145 (6)		
Other	71 (6)	3 (1)	217 (9)	245 (2)	200 (<1)
Oxylipins and Prostaglandins	6 (1)	15 (5)	76 (3)	254 (3)	
Flavonoids	7 (1)		4 (<1)	10 (<1)	4000 (11)
Coumarins			1 (<1)	1 (<1)	2000 (6)[e]
Total	1199	316	2543	9819	35210

Blunt and Monro's (2008) Dictionary of Marine Natural Products was used to assess chemodiversity of bacteria, micro-algae, macro-algae, and invertebrates. Vascular plant chemodiversity was estimated by Harborne (1988) and Wink (2003). We excluded fatty acids, sterols, carotenoids, polypyrroles, amines, nucleic acids, nucleo bases, polyacetylenes, waxes, cinnamic-acid derivatives, and carbohydrates. Blanks indicate that the compound is either not reported or not produced.

[a]Archae and Bacteria (including Cyanobacteria).

[b]Porifera, Cnidaria, Platyhelminths, Annelida, other Vermiforms Groups, Ectoprocta, Mollusca, Echinodermata, Arthropoda, Hemichordata, Urochordata, And Cephalochordata.

[c]Includes triterpenes, saponins, and steroids.

[d]Includes polyketides, and acetogenins.

[e]Includes phenylpropanoids, coumarins, and lignans.

marine herbivores in a seemingly idiosyncratic manner. Moreover, structurally similar compounds (e.g., dictyol E versus pachydictyol A) can have vastly different effects on a single herbivore (Supplementary Table 1). There are useful evolutionary hypotheses for why marine herbivores differ in feeding responses toward SMs, including phylogenetic history (Poore et al. 2008) and susceptibility to predation (Hay et al. 1987a; see Diet Breadth section), yet the biochemical mechanisms underlying most of this variation remain unexplained.

One likely explanation for the variation in the deterrence of feeding by herbivores is that it reflects variation in toxic, post-ingestive responses (Hay 1996; Paul et al. 2001). Typically, postingestive responses have been investigated by isolating herbivores on fresh tissue or artificial foods coated with crude extracts and measuring fitness (e.g. Lobel and Ogden 1981; Sotka and Hay 2002; Cruz-Rivera and Hay 2003; Taylor and Brown 2006). One problem with this approach is that it cannot separate a toxic effect of metabolites from the effect of lowering the intake of food. To date, only two studies have tested the toxic effects of macrophytes' metabolites while controlling for intake. Hay et al. (1987b) demonstrated that a warm-temperate herbivorous

fish (spottail pinfish, *Diplodus holbrooki*) had lowered growth rates when fed foods coated with a diterpene alcohol (pachydictyol A), relative to control foods, when feeding rates were controlled. In addition, Pennings and Carefoot (1995) intubated a sea hare (*Aplysia juliana*) to control for intake and demonstrated that an injection of pachydictyol A yielded no effect on growth rate.

There is little information on the ADME mechanisms that mediate post-ingestive consequences of macroalgal SMs. One set of studies examined enzyme responses (metabolism) when herbivores were intubated with lanosol, a brominated phenol produced by red algae. DeBusk et al. (2000) showed increased expression of a phase I enzyme isoform (cytochrome P450) and corresponding enzymatic activity in the chiton *Cryptochiton stelleri* after an oral injection of lanosol. A second study found no elevation in P450 activity in the chiton *Katharina tunicata*, nor in the abalone *Haliotis rufescens*, when exposed to lanosol (Kuhajek and Schlenk 2003) but did demonstrate increased activity of a phase II enzyme (glutathione S-transferase, or GST) in *K. tunicata*. These studies illustrate the idiosyncratic manner in which a single SM can illicit variable enzyme responses across species. In another line of studies, caulerpenyne, a sesquiterpene produced by the invasive green alga *Caulerpa taxifolia* induces higher activity of GSTs in a gastropod that consumed *C. taxifolia* (Sureda et al. 2009), as well as carnivorous fishes that either inhaled *Caulerpa*-infused seawater or consumed prey that grazed on *Caulerpa* (Uchimura et al. 1999). Caulerpenyne also appears to induce antioxidant enzymes within consumer tissues (Sureda et al. 2006, 2009).

Research focusing on the sequestration of SMs within the tissues of gastropods will provide an insight into ADME processes in marine consumers, as sequestration requires that the herbivore absorb, distribute, and (in some cases) metabolize SMs. Herbivorous opisthobranchs (sacoglossan sea slugs and anaspidean sea hares) sequester dietary compounds from chemically-rich green, red, and brown algae as well as from cyanobacteria (Wagele et al. 2006), distribute them to various tissues, and excrete or secrete them in response to attack or as a warning to potential predators (Faulkner 1992; Derby 2007). Herbivorous gastropods often concentrate SMs, including those that are extremely toxic, within the digestive gland. For example, the western Pacific sea hare, *Stylocheilus longicauda*, feeds on and accumulates cyanobacterial SMs from the genus *Lyngbya* (see Dinoflagellates and Cyanobacteria section). Even without access to analytical chemistry, residents of the local islands knew to avoid consuming the large, toxin-laden digestive gland to prevent death (Pennings and Paul 1993b). The digestive gland of the sea hare *Dolabella auricularia* causes vomiting, diarrhea, muscle-twitching and other neurological dysfunctions (Sorokin 1988) and consuming the sea hare, *Aplysia kurodai*, can cause liver damage (Sakamoto et al. 1998).

The enzymatic mechanisms that mediate absorption and storage of toxic SMs within sequestering opisthobranchs appear highly generalized, rather than evolved to counter particular structural SM classes. In a fascinating study, Pennings and Paul (1993b) isolated three species of sea hare with nine metabolites from a diversity of sources (macroalgae, cyanobacteria, and sponges) and structural classes (e.g. diterpene, sesquiterpene, brominated diphenol ether), some of which the sea hares likely never consumed in nature. Regardless of the identity of the metabolite or its structural class, ~80–90% of the metabolites were found within the digestive gland several days after consumption. These findings suggest that the digestive gland is not simply a transitory stop in the process of sequestration; rather, Pennings and Paul (1993) found that even after 39 days following cessation of feeding, virtually all of the compounds were maintained in the gland and without modification (Faulkner 1984; but see Rogers et al. 2000). Diet-derived compounds can be transformed before storage in some cases (Hay et al. 1987b; Pennings et al. 1996), but the transformed metabolites do not appear to be any more of a deterrent to generalist consumers than are the precursors (see also Pennings et al. 1999; Pennings et al. 2001). These patterns suggest that the opisthobranchs' generalist strategy of sequestration might represent an evolutionary solution to avoid autotoxicity (Wagele et al. 2006), to minimize the energetic costs of detoxification (e.g., Endicott and Ling 1989; Hildebrand et al. 2009), or both. If true, then any defensive benefit that sequestrated chemicals may additionally provide would represent an evolutionary "bonus." Distinguishing these hypotheses require that we characterize the ADME mechanisms underlying sequestration.

Dinoflagellates and Cyanobacteria

The chemodiversity of dinoflagellates and other phytoplankton (including diatoms, raphidophytes, and pyrmnesiophytes) is dominated by alkaloids, terpenes, and polyketides (Table 1). Dinoflagellates and cyanobacteria are the most notorious of these

microalgal groups because of the tendency of some of their species to produce harmful algal blooms or HABs. HABs are typically pelagic events that are termed 'red tides' or 'brown tides' because the water is pigmented from the high microalgal biomass. These blooms are associated with acute and elevated rates of mortality in populations of shellfish, fish, and mammals in marine (Landsberg et al. 2005), and freshwater habitats (Carmichael 2001). Only a fraction (~200 species) of the described dinoflagellates and cyanobacteria produce HABs, but their biological effects can be massive and contribute to several recognized syndromes of poisoning of humans (Van Dolah et al. 2001). As a consequence of the implications of HABs for human health, the literature on HABs is repleted with descriptions on chemodiversity and pharmacology (Shimizu 1993; Carmichael 2001; Landsberg 2002; Landsberg et al. 2005; Nicholson and Lewis 2006; Paul et al. 2007; Friedman et al. 2008; Paz et al. 2008; Pulido 2008; Wang 2008; Watkins et al. 2008). In contrast, the body of knowledge of the ecological functions and responses of HAB metabolites in non-human consumers has only recently been addressed (Hairston et al. 2001; Hay and Kubanek 2002; Bricelj et al. 2005; Doucette et al. 2005; Sarnelle and Wilson 2005; Pohnert et al. 2007; Berry et al. 2008; Camacho 2008). Here, we provide a flavor of this literature by focusing on a single genus within two groups of microorganisms (*Karenia* dinoflagellates and *Lyngbya* cyanobacteria), and the pharmacology and ecological roles of a single class of metabolite produced by each group (brevetoxins and lyngbyatoxin A, respectively).

Blooms of the dinoflagellate, *Karenia brevis*, in the Gulf of Mexico are among the oldest ever reported (Landsberg et al. 2005), and evidence indicates that the frequency and severity of these blooms have been steadily increasing over the past 50 years (Alcock 2007). The lipophilic polycyclic ethers (i.e., brevetoxins) cause "neurotoxic shellfish poisoning" or NSP, by binding to and activating voltage-dependent sodium channels. This induces violent neurological behaviors like convulsions, paralysis, and loss of equilibrium in fishes (Baden et al. 2005), and respiratory and circulatory distress in mammals (Baden 1989). Emerging ecological evidence indicates that brevetoxins lower consumption rates in several crustacean grazers (Paul et al. 2007), alter the behavior and fitness of rotifers (Kubanek et al. 2007) and copepods (Turner and Tester 1997; Landsberg et al. 2005; Prince et al. 2006; Breier and Buskey 2007; Cohen et al. 2007), and lower recruitment and growth in filter-feeding bivalves that consume *K. brevis* (Summerson and Peterson 1990; Keppler et al. 2006; Leverone et al. 2006; Haubois et al. 2007; Leverone et al. 2007). Despite these studies, ecological impacts remain understudied, in part because it is difficult to distinguish the relative importance of two routes of brevetoxin exposure, inhalation versus consumption (but see Poli et al. 2000; Tester et al. 2000). Additionally, because most studies utilize live *K. brevis* cells rather than artificial foods (Pohnert et al. 2007), it has been difficult to assess whether lowered fitness is due to an effect of the toxin or to due to starvation caused by a lowering of the rate of consumption of nutrients (Paul et al. 2007).

Cyanobacteria produce alkaloids (nearly 50% of reported compounds), peptides, terpenes, and polyethers. The two most commonly isolated categories of bioactive cyanotoxins are alkaloid neurotoxins (e.g., anatoxin-a) and cyclic peptide hepatotoxins (e.g., microcystins) (Burja et al. 2001). Cyanobacteria have long been a target of investigations in freshwater ecosystems (Hairston et al. 2001), but more recently, benthic marine cyanobacterial blooms produced by the genus *Lyngbya* have garnered attention because of their growing ecological impacts on nearshore tropical habitats (Paul et al. 2001). Arguably, more toxic metabolites are documented from *Lyngbya* species than for any other microalgal genus (Landsberg et al. 2005), numbering well over 100 (Burja et al. 2001; Osborne et al. 2001). One of these toxins, the indole alkaloid lyngbyatoxin, induces skin dermatitis and respiratory irritation in humans, as well as cytotoxicity, tumor promoter activity, and the activation of protein kinase C *in vitro* (Burja et al. 2001). Within marine ecosystems, lyngbyatoxin not only deters consumption by large generalist fishes, including rabbitfish and parrotfish, but is also a highly preferred food of small sea hares (e.g., *Steilocheilus striatus*) that sequester metabolites in their digestive glands (Paul et al. 2007; see also Cruz-Rivera and Paul 2006a). Mechanisms of ADME and the consequences for fitness of consuming *Lynbya* and its metabolites have yet to be explored.

Overall, the pharmacological effects of microalgal metabolites, especially those from HAB species, are better understood than are their ecological roles, while the reverse pattern emerges from the literature on macroalgal metabolites. This cross pattern suggests that ecologists working on microalgae–consumer interactions may face fewer hurdles in merging pharmacological and ecological approaches (Fig. 1) than will those working on other types of interaction.

Aquatic vascular plants

Knowledge of the chemical defenses of freshwater and marine vascular plants has lagged behind that for terrestrial vascular plants and marine macroalgae. The field started off slowly, in part, because nearly a century ago Shelford (1918) first asserted a view that aquatic vascular plants serve only as substrata for epiphytes and are consumed only after senescence and death, presumably because of their low nutritional content (Hutchinson 1975). It was only in the early 1990s that two influential reviews (Lodge 1991; Newman 1991) concluded that aquatic macrophytes are equivalent to terrestrial plants and marine macroalgae in nutritional (largely nitrogen) content and are consumed by a diverse array of generalist herbivores.

Since then, some progress has been made in uncovering the effects of SMs on grazing preferences among freshwater herbivores (Ostrofsky and Zettler 1986; Bolser et al. 1998; Burks and Lodge 2002; Cronin et al. 2002; Sodergren 2006; Miller and Provenza 2007). For example, Sodergren (2006) showed that selective herbivory by grass carp (*Ctenopharyngodon idella*) drives the composition of freshwater plant assemblages toward species that are chemically and structurally defended and nutritionally poor. Parker et al. (2007) showed that riverweed (*Podosternum ceratophyllum*) was preferred by the generalist herbivores Canada geese (*Branta canadensis*) and crayfish (*Procambarus spiculifer*) over an abundant and chemically-defended stream moss (*Fontinalis novae-angliae*), which harbored a species of amphipod (*Crangonyx gracilis*) and isopod (*Asellus aquaticus*) that tolerate moss SMs.

In most cases, the deterrent effects of alkaloids, glucosinolates, and polyphenolics have been indirectly inferred. For example, glucosinolates are nitrogen-containing and sulfur-containing compounds that occur in the order Capparales, including the Cruciferae (Louda and Mole 1991). One aquatic crucifer, watercress (*Nasturtium officinale*) is defended against a variety of herbivorous invertebrates, including caddisflies, snails, and amphipods, and evidence shows that the glucosinolate–myrosinase system of this plant acts as a chemical deterrent (Newman et al. 1992) and that it lowers growth rates of several herbivores (Newman et al. 1996). Phenolic acids (e.g., tannins, coumarins, and flavanones) are universally present in angiosperms and appear to deter feeding by some aquatic herbivores (Li et al. 2004). *Myriophyllum spicatum* had the highest tannin content among eight common submersed macrophytes assayed by Li et al. (2004), and its leaves were rejected by pulmonate snails in preference tests. However, Li and co-authors could not rule out other secondary compounds as being responsible for the low preference. In general and despite the growing recognition that herbivory on aquatic plants is common, we lack systematic efforts in assessing the chemical defenses of aquatic plants, their effects on the fitness of aquatic herbivores, and the ADME mechanisms employed. Moreover, there is virtually no work on the freshwater herbivores that regularly consume chemically-rich fruits and seeds, such as the numerous species of fishes of the flooded forests of Amazonia (Goulding 1980; Correa et al. 2007).

Among marine vascular plants, parrotfishes, turtles, urchins, and other large herbivores readily consume seagrass tissue (Hay et al. 1987b; Hughes et al. 2004; Goeckner et al. 2005; Heck and Valentine 2006). This suggests that the phenolic compounds within seagrasses (e.g., Buchsbaum et al. 1984; Vergeer and Develi 1997; Agostini et al. 1998) are generally ineffective against these larger herbivores, although few studies on isolated seagrass metabolites have been pursued (e.g., Harrison 1982).

Invertebrates

Most invertebrate phyla do not produce deterrent SMs (Berenbaum 1995), but several phyla (especially sponges and cnidarians) are industrious chemists (Table 1) (reviewed by Paul 1992b; Cimino and Ghiselin 2001; McClintock and Baker 2001; Blunt et al. 2008; Paul and Ritson-Williams 2008). Aquatic invertebrates generate alkaloids, terpenoids, and compounds from amino-acid and acetogenin pathways (Harper et al. 2001). Care must be given to assigning definitively the progenitor of a compound, as microsymbionts also produce a significant portion of putatively invertebrate SMs (Lopanik et al. 2004a, 2004b; Piel 2004, 2006; Dunlap et al. 2007; Grozdanov and Hentschel 2007).

Organisms within these chemically-rich invertebrate phyla tend to be sessile, conspicuous, or benthic (or some combination of these traits) and as a consequence, are highly susceptible to predators. Thus, many of invertebrates' SMs serve as chemical deterrents against consumers (Pawlik 1993; Cimino and Ghiselin 1998; Stachowicz 2001; Paul and Puglisi 2004). Chemical defenses have been reviewed for marine worms (Kicklighter et al. 2004; Kicklighter and Hay 2006), sponges (Pawlik et al. 1995; Burns et al. 2003), gorgonians (Pawlik et al. 1987; Coll 1992; O'Neal and Pawlik 2002), tunicates (Pisut and Pawlik 2002; Tarjuelo et al. 2002), and

molluscs (Avila 1995; Cimino and Ghiselin 1999; Garson 2006; Derby 2007). Other reviews of invertebrates' chemical defenses have also been organized by lifestyle—marine holoplankton (Bullard and Hay 2002), meroplankton (Lindquist and Hay 1996)—and locale (Amsler et al. 2001).

We have very few examples of postingestive consequences of consuming invertebrates' SMs (Stachowicz 2001). A study by Lindquist and Hay (1995) attempted to assess the impact of the didemnins, a group of cyclic depsipeptide compounds isolated from adults and larvae of the Caribbean tunicate, *Tridemnum solidum*, on the fitness of two generalist consumers. These compounds induced vomiting and learned aversion in the pinfish *Lagodon rhomboides*, yet no toxic effect could be quantified. The particle-feeding anemone, *Aiptasia pallida*, did not learn to avoid consuming didemnin-coated foods, and when didemnins comprised less than 2% of the total daily dietary intake of anemones, there was significantly reduced growth and clonal reproduction.

Many SMs from invertebrates have potent pharmaceutical properties, e.g., cytotoxicity, inhibition of protein synthesis, disruption of the cytoskeleton, transcription of regulatory inhibitors (reviewed by Rawat et al. 2006; Hill 2007; Blunt et al. 2008), and provide excellent starting points for ADME studies. For instance, the soft-bodied, carnivorous ribbon worms (phylum Nemertea) possess a variety of alkaloids that stimulate acetylcholine (ACh) chemoreceptors belonging to a superfamily of ion-gated channels that include the receptors of amminobutyric acid, glycine, and type 3 serotonin (Kem et al. 2006). This group of related lipophilic alkaloids can readily pass through membranes causing recoil behaviors or paralysis in a variety of invertebrates (marine annelids, crustaceans, and insects), likely through the stimulation of nicotinic cholinergic receptors on the appendages of its prey. Moreover, pyridyl alkaloids, isolated from worms, stimulated nicotinic receptors modulating chloride channels in the stomatogastric muscles of crayfish, a process that could interfere with the capture and digestion of prey (Kem and Soti 2001).

We have evidence that detoxification enzymes are employed by some marine carnivores to metabolize SMs produced by their invertebrate prey. Tropical butterflyfish consume soft corals (i.e., gorgonians) and are thus consistently exposed to terpenes (Rodriguez 1995) that induce specific isoforms of cytochrome P450 monooxygenases (or CYPs). Vrolijk et al. (1994) found highly specific content of total P450 in the livers of butterflyfish (*Chaetodon capistratus*) that consumed gorgonian corals. The high total P450 content is driven by changes in CYP families 2 and 3 (termed CYP2 and CYP3), which are thought to have evolved partially in response to exogenous metabolites (Gonzalez and Nebert 1990), and are known to metabolize a diverse range of lipophilic compounds, including dietary terpenes (Pass et al. 1999; Miyazawa et al. 2001; Pass and McLean 2002). In another study, two sympatric, congeneric butterflyfish species (*Chaetodon striatus* and *C. ocellatus*) that do not consume gorgonians were found to contain two-fold to three-fold less total P450 content and significantly less CYP2 and CYP3 proteins (Vrolijk et al. 1995). It has proven difficult to identify the P450 isoforms responsible for metabolism of dietary terpenes in butterflyfish (DeBusk et al. 2008).

A different strategy of metabolizing gorgonian SMs is employed by the Flamingo Tongue gastropod, *Cyphoma gibbosum*. Its digestive gland has low P450 content but high GST activity when collected from a number of gorgonian hosts (Vrolijk and Targett 1992). Whalen et al. (2008) traced this activity in two major mu-class and one minor theta-class GST isoforms related to mammalian prostaglandin-conjugating GSTs and dehalogenases. *Cyphoma*'s high constitutive expression of digestive-gland GSTs may protect this consumer from high concentrations of gorgonian SMs.

Some carnivorous gastropods sequester metabolites from prey. Nudibranch gastropods are often brightly-colored, lack a protective shell, and have the capacity to sequester metabolites from hydroids, bryozoans, tunicates, and soft corals within specialized tissues called mantle–dermal formations (MDFs) (Wagele et al. 2006). These tissues maintain metabolites at the distal surfaces of the animal, which makes them more available as a deterrent to predation by larger fish and by crustaceans (e.g., Avila and Paul 1997). Some nudibranchs also produce SMs *de novo* (Faulkner 1992; Kubanek et al. 2000) and tend to store these biosynthetic compounds in tissues or in subcellular compartments that differ from those harboring sequestered compounds (for exhaustive review see Wagele et al. 2006). Sequestered compounds are routinely transformed (Faulkner 1992) both enzymatically and non-enzymatically (Cutignano et al. 2004). The broader evolutionary issues that emerged in discussing sequestration of macroalgal compounds (see *Macroalgae* above) are equally relevant to nudibranchs sequestering invertebrate compounds.

Merging pharmacology and the evolutionary ecology of consumer–prey interactions

Several vexing issues in the ecology and evolution of aquatic consumer–prey interactions will benefit from understanding the biochemical mechanism that underlies consumers' responses (Fig. 1). Here, we outline a subset of these issues and, when possible, provide testable predictions for future investigations (Table 2). Many of these ideas center on marine macroalgal–herbivore interactions, in part, not only because of the background of the authors, but also because these interactions have arguably garnered the most attention in the aquatic literature.

The evolution of specialization

An understanding of ADME mechanisms provides a powerful framework for examining the ecology and evolution of dietary specialism versus generalism in aquatic consumers. The forces that drive the evolution of specialization among herbivores have been explored in terrestrial systems for decades (Dethier 1954; Ehrlich and Raven 1964), and recent insights into ADME have provided a mechanistic underpinning (Foley and Moore 2005; Li et al. 2007). The evolution of host use has been explored within marine systems only recently relative to terrestrial insects (Hay and Fenical 1988; Paul 1992a), yet it is already clear that seaweeds exert strong selection on the feeding choice, life history, morphology, and physiology of smaller, ''insect-like'' invertebrates termed ''mesograzers.'' For two decades, the role of lipophilic chemistry in the evolution of mesograzer range of hosts was heavily influenced by the ''enemy-free space'' hypothesis of Hay et al. (1987a). This theory predicts that small herbivores consume and inhabit seaweeds that are chemically-defended against larger, more mobile herbivores such as fishes and urchins (Paul 1988; Hay et al. 1990; Duffy and Hay 1991; Stachowicz and Hay 1999; Taylor and Steinberg 2005; Cruz-Rivera and Paul 2006b; see Parker et al. 2007 for a freshwater example).

Table 2 Important research questions that emerge from an integration of pharmacological approaches with the evolutionary ecology of marine consumer–prey interactions.

Evolution of specialization
• Do generalist herbivores have 'all-purpose' and promiscuous suites of biochemical mechanisms (i.e., ADME) to tolerate a broad range of algal SMs? Do specialists on chemically-rich seaweeds have highly-efficient and specific suites of ADME mechanisms? Do specialists on chemically-depauperate seaweeds have relatively low ADME capacity?
• Does population-level (Sotka and Hay 2002) and species-level variation in utilization of prey SMs (Cimino and Ghiselin 2001, Poore et al. 2008) reflect the differential evolution of ADME?
Generalist consumers and diet mixing
• Does the ability to detoxify macroalgal metabolites regulate intake rates and drive feeding preferences of generalist consumers (sensu Freeland and Janzen 1974)?
Nutrient-toxin interactions
• Are nutrient-SM interactions commonly part of coevolved defensive strategies of marine prey?
• To what extent do nutritional considerations constrain the evolution of ADME capacity in marine consumers?
Evolution of taste
• Are the taste responses of consumers to chemically-rich marine prey conserved across fish?
• What are the proximate chemical cues used by fish taste buds and how do they exert their effects ? How do these signals get translated into food choice?
Climate change and macroalgal–herbivore interactions
• How is macroalgal SM production affected by climate shifts in ultraviolet, temperature and pH? Will simultaneous changes in all these environmental variables yield additive or synergistic impacts on macroalgal chemistry?
• Do these changes translate to differential palatability to herbivores and foraging patterns?
• Which climate shifts will directly impact the physiology (including ADME) of aquatic herbivores? Does this shift alter herbivore response to macroalgae (e.g., via shifts in feeding tolerance)?
• Can we use these mechanisms to predict the response of local macroalgal communities to a changing climate?
Anthropogenic contaminants and consumer–prey interactions
• Is ADME capacity for SMs in prey altered by contaminants from anthropogenic sources and vice versa? Does the extent of cross-resistance depend on the chemical relatedness of natural products and contaminants?
• How does the evolution of tolerance to SMs differ from the evolution of tolerance to high levels of contamination?

An alternative role for lipophilic chemistry in the evolution of herbivores' diet breadth was recently proposed by Poore et al. (2008), who hypothesized that the primary evolutionary advantage for generalist consumers (large and small) in consuming chemically-rich prey is that it increases the number of appropriate seaweed hosts and thereby increases the available base of resources. To test this idea, Poore et al. (2008) compared the ranges of hosts of herbivores that consumed seaweeds with lipophilic SMs (e.g., diterpenes and acetogenins) versus the array of hosts for herbivores that did not consume these chemically-rich seaweeds. The authors focused on ascoglossan slugs (dietary specialists), ampithoid amphipods (variable foraging strategies), and fishes (dietary generalists). The results indicated that herbivores that include chemically-rich seaweeds in their diets feed on a broader range of algae relative to herbivores that avoid chemically-rich seaweeds (Poore et al. 2008). Specifically, fishes that consume seaweeds with lipophilic SMs dramatically increased their host range from ~3 to 12 genera, while ampithoid amphipods increased from ~1.5 genera to 5.5. These data support earlier arguments that evolving a tolerance to algal metabolites is not associated with a reduced ability to use other hosts (Sotka and Hay 2002). For the relatively specialized slugs, there was no difference in range of hosts among slugs that did and did not include chemically-rich seaweeds. This novel hypothesis highlights an interesting contrast between the diet of small terrestrial and marine grazers; among terrestrial insects and mammals, specialists tend to be associated with chemically-rich plants (Berenbaum et al. 1996; Sorensen et al. 2005), while among marine herbivores, generalists tend to be associated with chemically-rich seaweeds (Poore et al. 2008).

These patterns should be reflected in ADME capacity of marine specialist versus generalist herbivores. The ADME mechanisms of generalist amphipods and fishes should require an 'all-purpose', functionally versatile suite of enzymes, capable of preventing absorption (e.g. efflux transporters) or of metabolizing a broader range of algal SMs. In contrast, the fish and amphipod specialists that tend to avoid chemically-rich foods should have relatively lower ADME capacity. These predictions differ with sea slugs, who are nearly always specialists: slugs specializing on chemically-rich seaweeds should have a highly efficient and specific suite of ADME enzymes compared to slugs that specialize on chemically-depauperate seaweeds.

A related ADME prediction comes from the literature on herbivorous and carnivorous opisthobranchs. Derived lineages appear to utilize prey that are more chemically-rich and complex relative to more ancestral lineages (Cimino and Ghiselin 1998, 1999, 2001), suggesting that the underlying ADME mechanisms of sequestration of secondary metabolites among derived lineages is more complex than within more ancestral lines.

Generalist consumers and diet mixing

Despite the fact that most marine consumers are generalist feeders (Hay and Steinberg 1992; Poore et al. 2008), it remains unclear why these herbivores mix their diets. Several studies demonstrate that generalist marine consumers actively seek a mixed diet with enhanced preference for food types not recently encountered, e.g., amphipods, (Poore and Hill 2006), isopods (Pennings et al. 2000), gastropods, (Kitting 1980; Pennings et al. 1993), and urchins (Lyons and Scheibling 2007). There is also some evidence that consumers learn to avoid SMs that are repeatedly offered, suggesting a feedback between adverse physiological response and foraging behavior (Lindquist and Hay 1995; Thacker et al. 1997; Long and Hay 2006; Fig. 1). Longer-term tests of performance (growth, survival or fecundity) by consumers feeding on mixed-species versus single-species diets have provided varied support for the benefits of a mixed diet. Consumers may perform best on mixed diets, e.g., amphipods (Cruz-Rivera and Hay 2001), isopods (Hemmi and Jormalainen 2004), gastropods (Watanabe 1984; Pennings et al. 1993), and fishes (Lobel and Ogden 1981), but performance on the best single-species diet commonly matched performance on mixed diets (e.g., Steinberg and van Altena 1992; Cruz-Rivera and Hay 2001; Scheibling and Anthony 2001). However, it was recently suggested that when one integrates measures of performance (i.e., growth, fecundity and survival combined), marine consumers fed with a mixed diet have higher fitness than those fed with monospecific diets (Stachowicz et al. 2007).

Limitations on the abilities of animals to detoxify SMs in prey are frequently cited as one of the major reasons for the maintenance of a mixed diet (Freeland and Janzen 1974). The detoxification-limitation hypothesis predicts that consumers can maximize intake, and subsequent fitness, by actively selecting a mixed diet with non-overlapping detoxification pathways. An excellent example is the brushtail possum, *Trichosurus vulpecula*, which consumed greater quantities of two plants' SMs when offered in paired-choice assays than when either

were offered as a single diet, if and only if, those two compounds were metabolized via different biochemical pathways within the herbivore (e.g., phase I hydrolysis versus phase II conjugation) (Marsh et al. 2006). For marine consumers, it is unknown whether generalists' feeding strategies relate to limitations in detoxification (Freeland and Jenzen 1974) or other factors promoting a mixed diet (e.g., nutrient complementarity; Raubenheimer et al. 2005 or sensory-specific satiety; Provenza 1996), but an examination of the ADME mechanisms utilized by generalists should help reveal intriguing patterns.

Nutrient–toxin interactions

A growing body of research suggests that the evolution of defensive SMs and of responses by consumers cannot be understood in isolation from nutrition and, conversely, many questions in nutrition will benefit from an approach that integrates non-nutrient dietary components, like SMs (Raubenheimer and Simpson 2009). While this area has been most extensively researched in terrestrial systems, the phenomenon has also been established for marine systems. As might be expected, the interactive effects of dietary components are complex, involving diverse nutrients, SMs, and multiple modes of interaction.

In marine systems, one established mode of interaction is the defensive strategy by prey to reduce palatability by combining low nutrient content with the presence of SMs. For example, nudibranchs may exacerbate the effects of chemical defenses by decreasing the caloric value (in relation to water and ash) of their body tissues (Penney 2002), such that lower nutritional quality decreased the palatability of nudibranch SMs to a predatory crab. In other cases, dilution of nutrients might interact non-additively with SMs. For example, chemical defenses might be more (or only) effective in nutritionally low-quality foods (e.g. Duffy and Paul 1992). One mechanism underlying such non-additive effects is compensatory feeding. Many animals compensate for lower content of nutrients by increasing the rate of food consumption, and in doing so increase the amounts of ingested SMs in that same food (Raubenheimer 1992; Slansky and Wheeler 1992). Therefore, the presence of SMs might impede the ability of animals to compensate for low density of nutrients (Targett and Targett 1990; Cruz-Rivera and Hay 2003).

In addition to such impacts on intake, the interactive effects of nutrients and SMs might be exerted post-ingestively. The negative impacts of SMs may exacerbate when combined with nutritionally inferior diets, but ingestion of SMs may offset the costs of a nutritionally poor diet. For example, the negative impact of dictyols on the fitness of two species of amphipods (*Gammarus mucronatus* and *Elasmopus levis*) was greater when combined with diets of poor quality (Cruz-Rivera and Hay 2003). By contrast, dictyols increased survivorship in one species of isopod (*Paracerceis caudata*) and did so to a greater extent when combined with a nutritionally-inferior diet. Although the mechanisms were not determined, the authors suggested that dictyols might have benefited the animals indirectly, through their impact on deleterious microorganisms or parasites, or directly by supplementing nutrition.

A related mode of interaction is when the recent feeding history of an animal, as opposed to the nutrient content of its food, influences its susceptibility to SMs. For example, sea urchins (*Arbacia punctulata*) that were deprived of food for 3 days ingested foods containing the diterpenoid pachydictyol A, which they would normally avoid (Cronin and Hay 1996b). These experiments provide an example in which nutritional state acts at the behavioral level in altering the deterrent effects of SMs. Nutritional state also may act at the physiological and biochemical levels in altering the toxicity of SMs (e.g., Yang et al. 1992), although little is known about such alterations in marine systems (Ianora et al. 2006).

Another mode of interaction that is well established in both terrestrial and marine systems is when SMs lower the nutritional quality of foods by reducing the efficiency of nutrient assimilation. Phlorotannins are the predominant class of water-soluble SMs from brown algae and function by complexing dietary proteins and other macromolecules in the guts of conusmers (reviewed by Targett and Arnold 2001). Animals vary greatly in their susceptibility to phlorotannins, with some subsisting on foods that contain high levels of these compounds (up to 15% dry mass) (Paul et al. 2001). A range of factors is known to play a role in this differential susceptibility, including structure of the gut, gut pH, surfactants in the gut, gut microbial assemblages, and nutritional status (Horn 1992; Horn and Ojeda 1999; Targett and Arnold 2001).

Interactions between SMs and nutrients are diverse and complex, and pose challenges for researchers wishing to understand the mechanistic and functional bases of foraging, selection of diet, and the related performance outcomes. In many cases, even comprehensive nutritional analyses will not explain fully the foraging choices of consumers

(e.g. Neighbors and Horn 1991). Recent advances in nutritional ecology have provided a means for systematically teasing apart the individual and interactive effects of various dietary components on consumers, including nutrients and SMs. Simpson and Raubenheimer (2001) used geometrical analysis to investigate the interactive effects of protein (P), carbohydrate (C) and the polyphenolic compound tannic acid (TA) in locusts (*Locusta migratoria*). Results showed that dietary TA had no effect on survival when foods contained a balanced complement of carbohydrate and protein, but survival on TA-containing foods decrased as the macronutrient balance deviated from optimal. This outcome was true both for foods with excess P and foods with excess C, but interestingly, the mechanisms of action differed with the direction of imbalance. When foods contained a low P/C ratio, TA primarily reduced intake, but in foods with a high P/C ratio the main effect of TA was reduction of the efficiency of the utilization of protein. The geometrical approach has been used to model the effects of multiple macronutrients on algal consumption by a fish (*Girella tricuspidata*) (Raubenheimer et al. 2005), but has yet to be applied to nutrient–SM interactions in marine systems.

The evolution of taste

Understanding the mechanisms of gustation (taste) that underlie foraging responses will help predict feeding preferences and serve as an essential and complementary approach to ADME. This is because feeding-avoidance behaviors of large consumers are commonly mediated by taste (i.e., compounds stored on or within the prey) rather than smell, due to the fact that metabolites are often sequestered within membrane-bound vesicles and display poor volatility (Paul 1992a). Gustation is well developed in fishes having evolved some 500 million years ago (Hara 1993, 2007), and appears to be dedicated to responding instinctively to feeding cues (Sorensen and Caprio 1998). The basic cellular and biochemical components of taste appear to be highly conserved in vertebrate evolution and, thus far, only a small array of fish species (i.e. goldfish, catfish, salmon, and zebrafish) have served as model systems for vertebrate chemical senses (Sorensen and Caprio 1998).

It had always been assumed that predators reject chemically defended prey on the basis of an aversive response to taste, yet little evidence had been offered as to the mechanisms underlying this behavioral response. Assmann et al. (2000, 2004) found that brominated pyrrole alkaloids isolated from *Agelas* sponges deterred fish, likely because the compounds inhibited calcium influx into taste receptor cells (Bickmeyer et al. 2004). However, the ecological relevance of these assays remains in question because the choice of model system, rat adrenal cells, and sea hare neurons, may not be representative of chemo/olfactory reception in fish. Similarly, terpenes have been suggested to inhibit stimulation of the taste receptors of several terrestrial invertebrates (Gershenzon and Dudareva 2007). A study by Cohen et al. (2008) examined the chemoreception-signaling pathway, using a zebrafish model after first establishing that zebrafish, a freshwater species, presented aversive responses to sponge terpenoids similar to those of the well-studied reef fish *Thalassoma bifasciatum*. The receptors of zebrafish that are involved in recognition of sour and bitter tastes were reconstituted in frog cell lines (*Xenopus* oocytes) and showed an electrophysiological response when the sponge triterpenes (formoside and ectyoplasides A and B) were applied. These receptors may be conserved amongst predators susceptible to prey toxins, which means that prey that possess these defenses can deter a multitude of potential consumers. Such evolutionary conservation may help explain why extracts of sponges seem to be broadly deterrent to sympatric and allopatric predatory fishes, regardless of their geographic origin (Becerro et al. 2003).

Climatic change and macroalgal–herbivore interactions

We have argued that understanding the chemical mediation of interactions between macroalgae and herbivores requires information on ADME. These studies can be complicated by naturally-occurring variation of several abiotic stresses, including desiccation (Renaud et al. 1990; Cronin and Hay 1996b; Heaven and Scrosati 2004; Dethier et al. 2005), UV light (Cronin and Hay 1996b; Pavia et al. 1997; Fairhead et al. 2006; Swanson and Fox 2007), and elevated water temperature (Sotka and Giddens 2009). These stressors affect both prey (altering palatability of prey) and consumer (altering consumers' ability to avoid or tolerate chemically-rich prey) simultaneously, and their outcomes can be difficult to predict. Such research has been motivated in recent years by the recognition that the dynamics of particular abiotic variables (temperature, UV radiation, and pH) are changing as a consequence of global climatic change (Portner and Farrell 2008; Przeslawski et al. 2008). Here, we

outline what is known about the abiotic influences on chemical mediation of macroalgal–herbivore interactions, recognizing that ADME likely plays important but undescribed roles in each of these systems.

Global increases in seawater temperature are pervasive and have effected change in some nearshore systems (Stachowicz et al. 2002; Lesser 2004; Richardson and Schoeman 2004). For seaweeds, limited data suggest that increased thermal stress reduces concentrations of chemical defenses in some chemically-rich algae and make seaweeds more palatable to consumers. The red alga *Delisea pulchra* is particularly susceptible to bleaching disease in the summer months; at times up to 80% of individuals in sampled populations show visible signs of bleaching, likely as a result of thermal stress (Campbell and Poore, unpublished data). Bleached tissues are depauperate in the protective halogenated furanones, as a result, they are more susceptible to pathogenic microbial attack, and support higher numbers of local herbivores in comparison to healthy plants (Campbell et al., unpublished data). Seasonal bleaching episodes may therefore permit grazers with low or moderate tolerance to SMs to adjust their feeding patterns in ways that exploit bleached plants.

For marine herbivores, seawater temperature represents an important abiotic modifier of feeding rates by herbivores, as evidenced by the positive correlation of seawater temperature with feeding rates (Robertson and Lucas 1983; Wyban et al. 1995; Yee and Murray 2004; Floeter et al. 2005; O'Connor 2009). Yet, the effects of oceanic warming on the ecology of ectothermic herbivores likely will be complex and context-specific. Sotka and Giddens (2009) demonstrated that elevated seawater temperatures can alter foraging behavior toward chemically-rich foods, but that foraging responses will be dependent on the thermal history of herbivore populations and the foods that are offered. Such complexity in response to rising temperatures is mirrored in the literature on terrestrial herbivorous insects (Larsson 1989; Stamp and Yang 1996; Coley 1998; Bale et al. 2002; Bidart-Bouzat and Imeh-Nathaniel 2008). Interestingly, endothermic herbivores may respond more predictably to changes in ambient temperature through thermic effects of SMs that influence thermoregulation (McLister et al. 2004; Dearing et al. 2008).

In response to rising UV radiation, aquatic macroalgae induces production of phlorotannins that are capable of absorbing light in the UV range, effectively protecting plant cells from UV damage (Pavia et al. 1997; Pavia and Toth 2008 and references therein). Induction of phlorotannins and other compounds that minimize UV damage may have the indirect consequence of deterring consumers (Stachowicz and Lindquist 1997), a phenomenon known as cross tolerance (Stratmann 2003). Again, it is important to note that upper thresholds of stress likely exist at which palatability changes in surprising ways. For example, excessive amounts of desiccation and UV light causes unpalatable brown seaweeds to become more palatable, while palatable seaweeds appear to become unpalatable (Renaud et al. 1990; Cronin 2001; Dethier et al. 2005).

Global increases in atmospheric CO_2 increase toxicity and deterrency of SMs in terrestrial plants (Roth and Lindroth 1995; Lindroth 1996; Lindroth et al. 1997; Coley et al. 2002). To our knowledge, only a single study has explored the effect of elevated CO_2 gases on macroalgal chemical defenses. Swanson and Fox (2007) found that tissues from two kelp species (*Laminaria saccharina* and *Nereocystis luetkeana*) grew faster when dissolved CO_2 was elevated by two-fold relative to tissues within seawater with current CO_2 levels, suggesting that these algae are carbon-limited. In addition, elevated CO_2 treatment increased phlorotannin loads within kelp tissues relative to controls, but did not alter the relative palatability of kelp tissues to the gastropod herbivore *Tegula funebralis*.

Anthropogenic contaminants and consumer–prey interactions

The ubiquity and persistence of environmental contaminants could alter how aquatic consumers respond to abiotic stressors. That is, the detrimental effects of anthropogenic contaminants (e.g., heavy metals, petroleum, herbicides, pesticides, and personal care products) on the fitness of aquatic consumers can be quite severe (Peters et al. 1997; Livingstone 1998, 2001), but surprising non-additive effects can emerge when pollutants co-occur with elevated temperatures or UV radiation. For example, elevated metabolic rates at higher temperatures will increase the rate of at which water is pumped across the gills, which in turn accelerates the uptake of contaminants (Reist et al. 2006).

In addition, exposure to pollutants frequently induces a battery of ADME genes in aquatic organisms and potentially alters the capacity of those biochemical processes to eliminate other metabolites (Bard 2000; Snyder 2000; Smital et al. 2004; Taylor et al. 2005; Rewitz et al. 2006;

Timofeyev et al. 2007; Epel et al. 2008; Lee et al. 2008), in a process known as cross-resistance (Després et al. 2007). Specifically, efflux transporters (phase III pathway) purge cells of chemicals, but are inhibited by a wide variety of SMs from algae, tunicates, sea hares, and gorgonians (Suganuma et al. 1988; Chambers et al. 1993; Williams and Jacobs 1993; Aherne et al. 1996; Quesada et al. 1996; Schröder et al. 1998; Litman et al. 2001; Tanaka et al. 2002; Smital et al. 2004). For example, caulerpin from green algae in the genus *Caulerpa* inhibits P-glycoprotein-ATPase activity (Phase III enzyme) in sponges and mussels, and as a consequence, the toxicity of the pollutant tributyl-tin increases (Schröder et al. 1998). Similarly, aldehydes from diatoms act synergistically in increasing the sensitivity of brine shrimp to normally sub-lethal concentrations of copper (Taylor et al. 2005). These findings suggest that feeding studies from animals collected from highly contaminated field sites may be confounded by induction or inhibition of contaminants on ADME capacity in consumers.

In some cases, food could be the source of both dietary chemicals and contamination. For example, brown macroalgae readily accumulate heavy metals because of the high affinity between metals and the sulfated polysaccharides in their cell walls (Roberts et al. 2006, 2008a, 2008b). The mechanisms of metal tolerance by aquatic invertebrates has been widely studied (e.g., the role of metallothioneins was reviewed by Amiard et al. 2006), but the degree to which they affect the ability of aquatic herbivores to tolerate algal SMs is unknown. Experimental manipulation of levels of metals in algal tissues as carried out by Roberts et al. (2006) offers the opportunity to examine the interaction by varying levels of metals independently of the levels of natural products that may be present and avoids many confounding issues of interactions between dietary and environmental chemicals. An understanding of ADME capacity in consumers and knowledge of which chemicals inhibit and induce this capacity will assist ecotoxicologists in deciphering the effects of toxicants under field conditions and will assist ecologists in understanding feeding preferences of aquatic consumers in variably contaminated habitats.

Summary

Nearly 30 years of study on marine and freshwater systems have provided hundreds of examples in which SMs of aquatic prey alter the foraging behavior of consumers, their fitness, or both. The overwhelming pattern that has emerged from this literature is one of variation; aquatic consumers profoundly differ in feeding responses across individuals, populations, and species and in ways that are seemingly unpredictable. Given that these consumers can have tremendous impacts on the structure and function of ecosystems, researchers who wish to predict ecological impacts of consumers will require a mechanistic understanding of consumer foraging.

Previous studies have largely focused on the relationship between the presence of specific SMs in prey and the feeding preferences (e.g., Supplementary Table 1) and fitness responses exhibited by consumers. The pharm-ecological approach (Fig. 1) represents an extension of these studies, by attempting to understand how consumers influence the concentration of SMs in the body (via ADME) and the biochemical mechanisms by which SMs exert their effects (i.e., the site of action and response). Simultaneously with these efforts, we implore researchers to focus on other physiological and behavioral responses (e.g. resting metabolic rate, locomotor activity, growth, reproduction) that have received little attention. The task will not be simple: 'each and every one of these cases is likely to have unique features' as Brattsten (1992) warned when considering mechanisms of detoxification among herbivorous insects. Yet, it is our hope that understanding the pharmacology of aquatic consumers may help unravel their idiosyncratic patterns in feeding behaviors, and make the identification of functional roles of aquatic consumers more predictable (Table 2). The translation of variation in feeding responses into variation at the biochemical level represents one of the greatest challenges for aquatic chemical ecologists and their interdisciplinary collaborators.

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