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Chemical Defenses: From Compounds to Communities

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Abstract. Marine natural products play critical roles in the chemical defense of many marine organisms and in some cases can influence the community structure of entire ecosystems. Although many marine natural products have been studied for biomedical activity, yielding important information about their biochemical effects and mechanisms of action, much less is known about ecological functions. The way in which marine consumers perceive chemical defenses can influence their health and survival and determine whether some natural products persist through a food chain. This article focuses on selected marine natural products, including okadaic acid, brevetoxins, lyngbyatoxin A, caulerpenyne, bryostatins, and isocyano terpenes, and examines their biosynthesis (sometimes by symbiotic microorganisms), mechanisms of action, and biological and ecological activity. We selected these compounds because their impacts on marine organisms and communities are some of the best-studied among marine natural products. We discuss the effects of these compounds on consumer behavior and physiology, with an emphasis on neuroecology. In addition to mediating a variety of trophic interactions, these compounds may be responsible for community-scale ecological impacts of chemically defended organisms, such as shifts in benthic and pelagic community composition. Our examples include harmful algal blooms; the invasion of the Mediterranean by *Caulerpa taxifolia*; overgrowth of coral reefs by chemically rich macroalgae and cyanobacteria; and invertebrate chemical defenses, including the role of microbial symbionts in compound production.

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Abbreviations: DSP, diarrhetic shellfish poisoning; FP, fibropapillomatosis; LTA, lyngbyatoxin A; OA, okadaic acid; PDBu, phorbol dibutyrate; PKC, protein kinase C; PKS, polyketide synthase.

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Introduction

This virtual symposium focuses on "the neuroecology of chemical defenses," which we emphasize throughout our review. Although we have selected some of the best-studied marine natural products for our discussion, neuroecological studies have been conducted on few marine natural products, and little information is available on this topic. We point out the many gaps in our understanding of this subject. To provide a comprehensive review of these marine natural products, we focus on advances in understanding their biosynthesis, mechanisms of action, and chemical ecology, and we discuss several examples of the importance of chemical defenses in altering the community ecology of marine habitats and ecosystems.

Marine Microalgae: Okadaic Acid and Brevetoxins

Many secondary metabolites produced by dinoflagellates exhibit a diverse array of potent biological activities (Shimizu, 1993). Perhaps the best-publicized metabolites are those that contribute to neurotoxic (NSP), paralytic (PSP), amnesic (ASP), and diarrhetic (DSP) shellfish poisoning syndromes in humans (Yasumoto and Murata, 1993). Although most of the causative toxins and their mechanisms of action are known, the ecological functions and consequences of these compounds are just beginning to be understood (Smayda, 1997; Wolfe, 2000; Hay and Kubanek, 2002; Landsberg, 2002; Zimmer and Ferrer, 2007).

Okadaic acid

Okadaic acid (OA) and its analogs are the polyether toxins responsible for most DSP-related illnesses (Fig. 1). While much work has focused on their pharmacological mechanisms of action (Haystead *et al.*, 1989; Schonthal and Feramisco, 1993), biochemical detection methodologies (Zhou and Fritz, 1994; Quilliam *et al.*, 1996; Quilliam and Ross, 1996), and the impacts of OA on aquaculture and

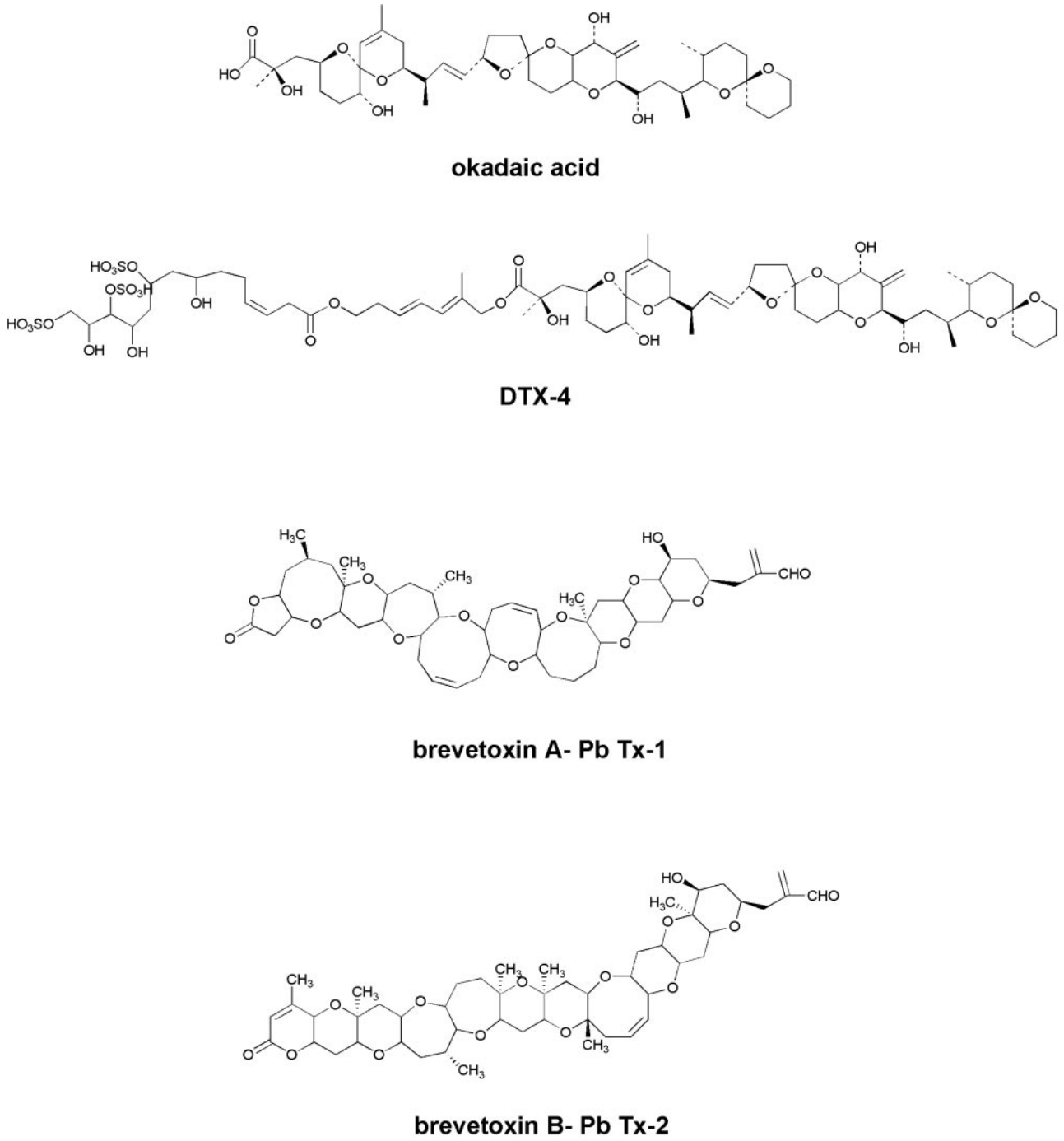


Figure 1. Structures of compounds in marine microalgae.

human health (Aune and Yndstad, 1993; Svensson, 2003), the ecological functions of OA still remain elusive. Okadaic acid was initially isolated and characterized from the sponges *Halichondria okadai* and *H. melanodocia* (Tachibana *et al.*, 1981). However, the source of OA and its analogs is now accepted as stemming from dinoflagellates belonging to the genera *Prorocentrum* and *Dinophysis* (Yasumoto *et al.*, 1987; Zhou and Fritz, 1994; McLachlan *et al.*, 1997).

The biosynthetic origin of OA has received considerable attention, especially from the theoretical standpoint. Unfortunately, radiolabeled feeding studies have proven to be quite difficult since *Prorocentrum* and *Dinophysis* are very selective genera that undergo autotrophic and heterotrophic metabolism (Izumikawa *et al.*, 2000; Daranas *et al.*, 2004). Daranas and colleagues suggested (2004) that the carbon skeleton of OA is synthesized by an unusual route regarding

the direct condensation reactions (acetate, proprionate, or butyrate units) associated with polyethers of terrestrial origin. Those authors believed that the parent compound is assembled from a polyketide chain, with glycolate as a starter unit and subsequent additions of acetate (Daranas *et al.*, 2004). The involvement of the tricarboxylic acid cycle in incorporating polyketide fragments into a polyether backbone is unusual and is characteristic of the biosynthesis of dinoflagellate toxins (Shimizu, 1993). Unfortunately, this biosynthetic route cannot be confirmed since attempts to incorporate metabolic precursors have had limited success, and further studies are necessary.

The actual producer of OA also remains unclear. No reports have identified the biosynthetic pathway of any secondary metabolite of dinoflagellate origin at the genomic level (Snyder *et al.*, 2005). Although immunological evidence suggests that bacteria inside the sponge *Suberites dumuncula* as well as sponge cells and intracellular vacuoles all contain OA (Wiens *et al.*, 2003; Schröder *et al.*, 2006), no bacteria that produce a polyketide toxin have been isolated from a dinoflagellate (Wiens *et al.*, 2003; Snyder *et al.*, 2005).

Okadaic acid acts as a potent inhibitor of protein phosphatases (Yasumoto *et al.*, 1987) and as a result has emerged as a valuable tool for the study of phosphorylation-based processes of cellular signaling (Douney and Forsyth, 2002). The protein serine/threonine phosphatases are a unique family of enzymes that catalyze the specific dephosphorylation of phosphoserine or phosphothreonine residues in many cell types. This family has been divided into four subcategories (PP-1, PP-2A, PP-2B, and PP-2C) on the basis of their substrate utilization and sensitivity to inhibitors (Cohen, 1989). The catalytic subunits of three of these phosphatases (PP-1c, PP-2Ac, and the A subunit of PP-2B) constitute a single gene family, termed the PPP gene family. Okadaic acid is a direct inhibitor of this group, in particular the PP-1c and PP-2Ac catalytic subunits (Holmes and Boland, 1993; Sheppeck *et al.*, 1997). The potent activity of OA is remarkably conserved across phyla: this toxin inhibits phosphatase activity in mammals, yeast, and higher plants (Cohen *et al.*, 1990).

One of the dinoflagellate sources of OA, *Prorocentrum lima*, possesses both OA-sensitive PP-1c and PP-2Ac activities (Dawson and Holmes, 1999). The question arises of how this dinoflagellate avoids autotoxicity from OA. Immunolocalization shows that OA in *P. lima* occurs in peripheral chloroplasts and may be affiliated with hydrophobic membranes (Zhou and Fritz, 1994). This location is considered insensitive to OA since only trace amounts of PP-1 and PP-2A have been detected in chloroplasts and are therefore unlikely to be directly involved in regulating chloroplast metabolism (Siegl *et al.*, 1990). One explanation for the lack of autotoxicity is that OA is sequestered away from the major phosphatase pool. Another hypothesis is that OA exists as a series of less active sulfated precursors that are capable of safely bioaccumulating within the host (Hu *et al.*, 1995).

Interestingly, most of the intracellular toxin in *P. lima* is in the form of the hydrophilic molecule DTX-4, which the results of metabolic labeling studies have suggested to be a biosynthetic precursor of OA (Needham *et al.*, 1995; Quilliam and Ross, 1996) (Fig. 1). According to Windust *et al.* (2000), DTX-4 can come into contact with other organisms in the environment by two routes. One route is excretion of DTX-4 as a sulfated ester derivative, followed by immediate hydrolysis to the OA diol-ester. The diol-ester moiety may be further hydrolyzed (much more slowly) to the free acid OA (Hu *et al.*, 1995; Quilliam and Ross, 1996). The second route is release of DTX-4 after cellular destruction through grazing or cell death. The enzymatic hydrolysis of DTX-4 to the uncharged hydrophobic OA diol-ester is an important step in the transfer and toxicity of these compounds. The transformation of precursor compounds to esterified derivatives could promote entry into cellular membranes in any number of co-occurring organisms and subsequently affect food-web dynamics.

While much is known about the mechanism of action of OA, the ecological and physiological effects of the toxin on other organisms remain poorly understood. The accumulation of OA in filter-feeders and the resulting impacts on human DSP-based illnesses have been well documented (Landsberg, 2002), but the uptake of OA through other trophic pathways and its subsequent ecological impacts have not been addressed in the same detail.

Judging from its broad activity, OA may serve as an allelopathic metabolite. Upon incubation with several marine microalgal species, micromolar concentrations of OA were capable of inhibiting the growth of all nontoxic species. However, *P. lima* itself was not affected by the addition of exogenous OA, even at much higher concentrations of the toxin (Windust *et al.*, 1996). Other work has demonstrated that although *P. lima*-preconditioned media does indeed contain allelopathic properties against naturally co-occurring dinoflagellates, the active fractions are not associated with OA (Sugg and Van Dolah, 1999).

The function of OA in sponges is not well understood. Studies by Wiens *et al.* (2003) have provided evidence for at least two putative roles of OA within the sponge *Suberites domuncula*. At low concentrations (<100 nmol l^{-1}), OA triggers a MAP kinase p38-regulated defense system against bacteria. At elevated concentrations (>500 nmol l^{-1}), OA acts as an apoptogen and promotes expression of the pro-apoptotic caspase gene with a simultaneous down-regulation of the expression of the anti-apoptotic *Bcl-2* homolog gene. In subsequent studies of *S. domuncula*, Schröder *et al.* (2006) suggested that OA may serve as a defense molecule by inducing apoptosis in symbiotic or parasitic annelids. In other work, Müller *et al.* (2007) demonstrated that OA is

required for the expression of the heat shock protein hsp70 at low temperature and contributes to cold tolerance in the sponge *Lubomirskia baicalensis*. The putative regulatory roles of OA in its host consortia are just starting to be examined.

It has been hypothesized that because *Prorocentrum* spp. are generally associated with benthic organisms such as seagrass and macroalgae, grazers foraging on these items may incidentally ingest the microalgae while feeding and thus be exposed to OA. Such a route of transmission has been documented in green sea turtles (*Chelonia mydas*) that feed on macroalgae in the Hawaiian Islands (Landsberg *et al.*, 1999). In addition, a single study has documented the presence of OA in a higher trophic animal, the carnivorous barracuda *Sphyraena barracuda* (Gamboa *et al.*, 1992). These studies exemplify the potential for OA uptake by herbivores and the opportunity for trophic transfer through the food chain. However, the route of OA transmission and the effects of OA on other marine organisms have not been assessed in most systems (Landsberg, 2002).

Cruz-Rivera and Villareal (2006) suggested that the palatability of macroalgae that are epiphytized by the ciguatoxin-producing dinoflagellate *Gambierdiscus toxicus* influences the flux of toxins entering marine food webs. They hypothesize that where dinoflagellates are located on rapidly consumed algae, even at low densities, large amounts of toxin might be consumed by herbivores, whereas dinoflagellates on ubiquitous but unpalatable algae would contribute little to the flux of toxins in marine food chains. This may also be the case for OA-producing organisms such as *Prorocentrum* spp.

The fact that OA enters and moves through various food chains suggests that many animals may be exposed to its physiological effects. OA is known to promote tumors in mice (Fujiki *et al.*, 1989; Sakai and Fujiki, 1991; Fujiki and Suganuma, 1993) and is hypothesized to do so in other animals (Landsberg, 2002). The only study to address the hypothetical role of OA as a natural tumor promoter in wild animals found that *Prorocentrum* spp. that produce OA were present on seagrass and algae consumed by sea turtles in the Hawaiian Islands, where a high proportion of the populations suffer from fibropapillomatosis (FP), a debilitating neoplastic disease linked to an oncogenic virus (Herbst, 1994). In that study, locations where FP was prevalent in the turtle populations were associated with areas where *Prorocentrum* spp. were abundant and widespread. In addition, the presence of presumptive OA in turtle tissue indicated that the turtles were exposed to OA and demonstrated a potential role of OA in the etiology of FP (Landsberg *et al.*, 1999). Similar mechanisms may also occur in diseases of shellfish, fish, and other wild animals.

Studies on the effects of OA on phytoplankton grazers have yielded mixed results, and it is hypothesized that OA is potentially toxic to some copepod grazers (Carlsson *et al.*, 1995; Maneiro *et al.*, 2000). Although OA has been detected in some zooplankton fractions, the concentrations are much lower than expected from the amount of toxin theoretically ingested. Thus, while copepods may act as vectors of DSP toxins to higher trophic levels, the amount of these toxins that copepods transport in the food web may be limited (Kozlowsky-Suzuki *et al.*, 2006). Dinoflagellate cell toxicity varies widely with environmental conditions (McLachlan *et al.*, 1994; Morton *et al.*, 1994), between species and strains (Lee *et al.*, 1989), and with habitat and life cycle (Pan *et al.*, 1999; Souto *et al.*, 2001), but it is not clear how this variation in OA production influences its ecological effects and community-level impacts.

Brevetoxins

The community-scale impacts of other dinoflagellate blooms have been better documented. For example, *Karenia brevis* (ex *Gymnodinium breve*, ex *Ptychodiscus brevis*), which causes red tides in Florida, produces brevetoxins—neurotoxins responsible for neurotoxic shellfish poison (NSP)—in humans that consume contaminated shellfish (Poli *et al.*, 1986; Morohashi *et al.*, 1999). Brevetoxins represent a suite of cyclic polyether compounds produced by *K. brevis* and the raphidophyte *Chattonella* cf. *verruculosa* (Poli *et al.*, 1986; Shimizu, 1986; Bourdelais *et al.*, 2002), including as many as 12 compounds (designated PbTx-1, −2, −3, *etc.*) ranging in molecular weight from 868 to 936 (Baden *et al.*, 2005) (Fig. 1).

Studies by Snyder *et al.* (2005) have offered enticing leads with the first definitive evidence for resident polyketide synthase (PKS) genes associated with the brevetoxin-producing dinoflagellate *K. brevis* and associated bacteria. A combination of flow cytometry, polymerase chain reaction, and fluorescence *in situ* hybridization were used to localize three PKS-encoding genes; two genes were localized exclusively within *K. brevis* cells, and a third gene was localized to *K. brevis* and associated bacteria (Snyder *et al.*, 2005). Evaluation of the genomic organization of PKS-encoding gene clusters has advanced our understanding of the mechanisms of polyketide biosynthesis in a number of biological systems (Staunton and Leadlay, 1995; Tillett *et al.*, 2000; Hill, 2006) and will also facilitate our understanding of the biosynthesis of polyethers in dinoflagellates.

Brevetoxins bind to voltage-gated sodium channels, causing repetitive depolarization of nerve cell membranes and interference with neuronal electrical impulses. In marine mammals and fish, death results most frequently from respiratory failure (Baden, 1983; Baden and Trainer, 1993; Purkerson *et al.*, 1999; Baden *et al.*, 2005; Bourdelais *et al.*, 2005). The potency and impacts of these neurotoxic mechanisms are evident on many trophic levels during harmful algal blooms (Turner and Tester, 1997; Landsberg, 2002).

Extensive blooms of *K. brevis* occur regularly in the Gulf

of Mexico (Tester and Steidinger, 1997; Kirkpatrick *et al.*, 2004) and cause massive die-offs of fish and birds, closures of shellfish beds, and strandings and deaths of manatees and turtles (O'Shea *et al.*, 1991; Hopkins *et al.*, 1997; Tester and Steidinger, 1997; Bossart *et al.*, 1998; Landsberg and Steidinger, 1998; Kreuder *et al.*, 2002; Flewelling *et al.*, 2005). The impacts of brevetoxins differ among organisms, particularly invertebrates, with some common organisms completely absent after a *K. brevis* bloom and others apparently unaffected (Turner and Tester, 1997; Landsberg, 2002).

Zooplankton are known to differentiate among phytoplankton and are affected by chemical defenses (Turner and Tester, 1997); however, the impacts that brevetoxins in *K. brevis* blooms have upon the zooplankton are complex and currently unclear. Some studies have found *K. brevis* to be acutely toxic to zooplankton grazers (Sykes and Huntley, 1987), while others have demonstrated avoidance behavior in zooplankton offered a diet of brevetoxin-producing dinoflagellates (Huntley *et al.*, 1986; Turner and Tester, 1989). Further studies have demonstrated that exposure to *K. brevis* reduces fecundity in copepod grazers (Turner *et al.*, 1998; Collumb and Buskey, 2004). However, whether these observations were due to a toxic effect of the brevetoxins or resulted from starvation or the low nutritional value of the *K. brevis* is unclear (Breier and Buskey, 2007). Both Breier and Buskey (2007) and Prince *et al.* (2006) found that although *K. brevis* was not toxic to the copepod *Acartia tonsa*, the low nutritional value of the dinoflagellate prevented the copepod grazer from producing normal offspring. In a study comparing two rotifer grazers, *K. brevis* was eaten by the rotifers only when it was offered as part of a mixed diet, and *Branchionus plicatilis* fed on the mixed diet only after 3 or 4 days (Kubanek *et al.*, 2007). *Karenia brevis* directly impacted rotifer fitness by decreasing egg production and population growth to the same levels as in starved rotifers. Neither rotifer—*B. ibericus* (sympatric with *K. brevis*) or *B. plicatilis* (allopatric)—ingested *K. brevis* as a sole diet. The presence of organic cellular extracts, but not the isolated brevetoxins PbTx-2, PbTx-3, and PbTx-9, deterred feeding in *B. plicatilis* (Kubanek *et al.*, 2007). Further research is required to fully understand the implications of *K. brevis* blooms on the zooplankton community and the effects of neurotoxins on these herbivorous grazers.

Because of the direct concern to fisheries, the impact of brevetoxins has been better studied on co-occurring vertebrates than on invertebrates. Fish kills associated with red tides have been estimated to be up to 100 tons of fish per day (Kirkpatrick *et al.*, 2004), with fish dying as a result of lack of muscle coordination, paralysis, convulsions, and respiratory failure (Kirkpatrick *et al.*, 2004). Fish kills occur even at low concentrations when cells lyse and the toxin is absorbed across the gills (Baden, 1988), resulting in high mortalities during blooms (Baden and Mende, 1982; Kirkpatrick *et al.*, 2004). Routes of exposure in vertebrates include direct ingestion of toxin-producing cells, accumulation through trophic pathways, and direct exposure to extracellular toxin in the water column (often associated with bubbles) through gill exposure in fish or inhalation of aerosolized brevetoxins in humans and marine mammals (McFarren *et al.*, 1965; Abbott *et al.*, 1975; Fleming *et al.*, 2005; Pierce *et al.*, 2005; Woofter *et al.*, 2005).

Brevetoxins can move through marine food webs, as was demonstrated in toxin transfer from dinoflagellates to copepod grazers and to juvenile fish (Tester *et al.*, 2000). The neurotoxins can also accumulate in high concentrations in seagrass and fish, which act as vectors for the bioaccumulation of brevetoxins in herbivorous manatees and piscivorous dolphins, respectively (Flewelling *et al.*, 2005). Brevetoxins accumulated in omnivorous and planktivorous fish during feeding trials in which the fish were fed toxic shellfish and *K. brevis* cultures with low concentrations of extracellular brevetoxin. Fish remained healthy while brevetoxin accumulated in tissues from a food source, and thus they served as a mechanism for trophic transfer of toxins (Flewelling *et al.*, 2005). Recent evidence suggests that brevetoxins and their metabolites may be transported through the placenta from mother to offspring in mammals, although the implications of this finding are still inconclusive (Benson *et al.*, 2006). Abnormalities have been observed in the development of fish embryos after the eggs were exposed to PbTx-1. After hatching, morphological abnormalities included lateral spine curvature, herniation of brain meninges, and defects in the skull. At doses higher than 4.1 ng per egg, embryos developed but failed to hatch. Given the similarity between higher and lower vertebrates in developmental processes, this study has identified the potential for teratogenic effects of brevetoxin across multiple phylogenetic classes (Kimm-Brinson and Ramsdell, 2001).

The trophic bioaccumulation of dinoflagellate toxins such as OA and brevetoxins suggests that harmful algal blooms have a greater impact at the community level than was previously thought. As stated by Hay and Kubanek (Hay and Kubanek, 2002), "The crucial ecological question as to why many microalgal species produce potent neurotoxins remains unanswered, although these compounds clearly have dramatic consequences on populations of many marine species, on community structure and often on ecosystem function."

Marine Benthic Cyanobacteria and Macroalgae: Lyngbyatoxin A and Caulerpenyne

Lyngbyatoxin A

More than 100 biologically active secondary metabolites have been isolated from the cyanobacterial genus *Lyngbya* (Burja *et al.*, 2001; Gerwick *et al.*, 2001; Osborne *et al.*, 2001). Most studies have concentrated on the isolation of

novel compounds, with a focus on their biomedical potential and pharmacological applications; however, a few studies have addressed the ecological roles of these compounds (Paul *et al.*, 2001).

Lyngbyatoxin A (LTA) is an indole alkaloid that was first isolated from *Lyngbya majuscula* collected in the Hawaiian Islands, where it caused potent skin irritation in swimmers who came into contact with it (Cardellina *et al.*, 1979) (Fig. 2). In humans, LTA causes contact dermatitis; these health impacts are thoroughly reviewed by Osborne *et al.* (2001) so will not be discussed further here. Lyngbyatoxin A and its analogs are structurally and pharmacologically related to the teleocidins produced by *Streptomyces* spp. *Lyngbya majuscula* produces a wide variety of secondary metabolites, and LTA production varies among collections from different locations worldwide. For example, it has been isolated from *L. majuscula* in Hawaii (Cardellina *et al.*, 1979), Australia (Capper, 2004; Osborne, 2004), Guam (D. Nagle and V. Paul, unpubl. results), and Japan (Izumi and Moore, 1987), but has not yet been detected in *Lyngbya* collections from Florida (Paul *et al.*, 2005). Whether this is due to genetic variation in *L. majuscula* or is a result of environmental factors is unclear.

The gene cluster responsible for LTA production has been identified, making it possible for future studies to determine whether differential production of LTA among geographically distinct *L. majuscula* populations is due to environmental up-regulation of toxin biosynthesis or genetic differences across *L. majuscula* strains. The gene cluster is a nonribosomal peptide synthetase (NRPS) system spanning 11.3 kb with four open reading frames, including a novel aromatic prenyltransferase (Edwards and Gerwick, 2004), which is hypothesized to catalyze the conversion of the LTA precursor in the final step of biosynthesis (Irie *et al.*, 1984; Edwards and Gerwick, 2004).

Lyngbyatoxin A is a potent tumor promoter in mice (Cardellina *et al.*, 1979; Fujiki *et al.*, 1983). In the presence of an initiating agent (dimethylbenzoic acid), the application of LTA resulted in a tumor incidence of 80% in treated mice 21 weeks after application (Fujiki *et al.*, 1983). Lyngbyatoxin A exerts biological activity through the activation of protein kinase C (PKC), a multifunctional kinase that phosphorylates serine and threonine residues on many target proteins. PKC coordinates a wide variety of cellular processes *via* signal transduction (Webb *et al.*, 2000; Spitaler and Cantrell, 2004), including those involved in development (Otte *et al.*, 1991), memory, proliferation (Murray *et al.*, 1993), carcinogenesis (Ashendel, 1985), and differentiation (Cutler *et al.*, 1993).

The ecological functions of the biologically active secondary metabolites produced by *L. majuscula* are not clearly understood, but LTA has been shown to be toxic to fish (Cardellina *et al.*, 1979), and several *Lyngbya* metabolites deter grazing in potential generalist herbivores (Nagle and Paul, 1998, 1999; Paul *et al.*, 2001; Cruz-Rivera and Paul, 2007). While some animals may utilize *L. majuscula*

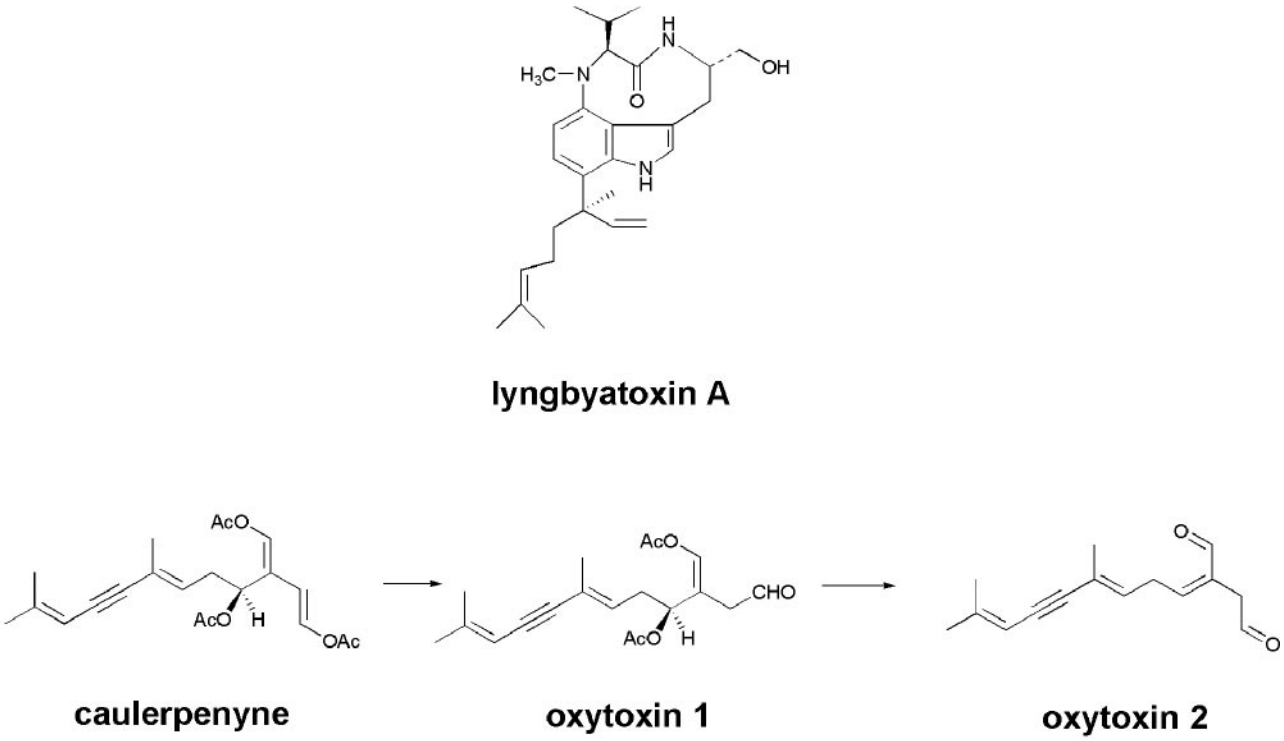


Figure 2. Structures of compounds in marine benthic cyanobacteria and macroalgae.

as a refuge from predation, most do not selectively forage on *L. majuscula*, and secondary metabolites apparently render this ephemeral food source unpalatable to most generalist grazers (Nagle *et al.*, 1996, 1998; Pennings *et al.*, 1996; Capper *et al.*, 2006a; Cruz-Rivera and Paul, 2007). Several studies have noted that herbivorous rabbitfish avoid feeding on *L. majuscula* containing LTA and other secondary metabolites such as ypaoamide, malyngamides, and malyngolide (Nagle *et al.*, 1996; Thacker *et al.*, 1997; Nagle and Paul, 1998; Capper *et al.*, 2006c). However, specialist grazers, including the opisthobranch mollusc *Stylocheilus striatus*, feed voraciously and grow well on *Lyngbya* spp. (Paul and Pennings, 1991; Pennings *et al.*, 1996; Capper *et al.*, 2006a, b; Cruz-Rivera and Paul, 2006, 2007; Capper and Paul, in press).

Stylocheilus striatus has been relatively well studied for its consumption of *L. majuscula*. In laboratory assays, crude extracts from *L. majuscula*, containing LTA, deterred feeding by amphipods, urchins, crabs, and rabbitfish (Capper *et al.*, 2006a). In contrast, crude extracts of *L. majuscula* stimulated feeding in *S. striatus* (Capper *et al.*, 2006a, b; Capper and Paul, in press). The sea hares *S. striatus* and *Bursatella leachii* consumed *L. majuscula* with LTA preferentially over a range of other algal species. When fed an exclusive diet of *L. majuscula* for 10 days, both sea hare species grew well, although growth rates and conversion efficiency rates of cyanobacterial mass to body mass varied between species. This difference may have been related to sea hare age, growth potential, and ability to acquire or detoxify secondary metabolites (Capper *et al.*, 2006b). In addition, *S. striatus* offered three different chemotypes of *L. majuscula* fed selectively on *L. majuscula* containing only LTA rather than a second strain containing both LTA and debromoaplysiatoxin (DAT) (Capper *et al.*, 2006b). As DAT did not deter feeding by *S. striatus* under natural concentrations (Nagle *et al.*, 1998), it is likely that the cumulative effect of the toxins (or other unidentified compounds), rather than merely the presence of DAT, may be driving this selectivity (Capper *et al.*, 2006b).

To test whether grazers acclimate to chemically defended prey or have physiologies that are adapted to these toxins, Capper *et al.* (2006a) examined the feeding behavior of co-occurring and allopatric consumers feeding on *L. majuscula.* The study demonstrated that LTA deterred generalist grazers regardless of their foraging history. Alternatively, specialist grazers such as *S. striatus*, even those with no prior experience of LTA, were stimulated to feed, indicating that this herbivore was adapted to feed on LTA without prior exposure.

In addition to selective foraging on *L. majuscula* containing LTA, a number of opisthobranchs, including the sea hares *S. striatus* and *B. leachii* and the cephalaspidean *Diniatys dentifer*, sequester LTA. In all three of these consumers, the primary repository for LTA was the digestive gland; however, small concentrations of LTA were also found in the ink, fecal matter, and body tissue (Capper *et al.*, 2005). The role of toxin sequestration for defense by all sea hares has been debated, since internal storage of toxins derived from diet provides little protection from predators (Pennings *et al.*, 2001). Alternatively, storage of secondary metabolites in skin or ink may deter feeding without the sea hares being consumed (Pennings and Paul, 1993). However, inking is not only for defense and probably has multiple ecological roles in sea hares (Derby, 2007). Other *L. majuscula* secondary metabolites, such as malyngamides and majusculamides, are also sequestered to the sea hare digestive gland, where they are transformed to less harmful acetates (Pennings *et al.*, 1996, 1999). This may also be the case with LTA, because less toxic LTA acetates have been isolated from *S. striatus* (Kato and Scheuer, 1976; Gallimore *et al.*, 2000), suggesting that internal storage of high concentrations of diet-derived compounds may be primarily for detoxification purposes rather than self defense (Pennings *et al.*, 1999).

Generalist consumers are usually deterred by secondary metabolites produced by *Lyngbya* spp. Rabbitfish (*Siganus fuscescens*) and parrotfish (*Scarus schlegeli*) offered food containing the *Lyngbya*-derived compounds malyngamides A and B were deterred more during continuous feeding assays than during periodic assays, suggesting that hungrier fish less readily reject foods containing deterrent compounds and that longer exposures provide greater opportunity to learn of the deterrent compounds. Nevertheless, fish continued to sample the toxic food, perhaps as a mechanism to find cyanobacteria containing lower concentrations of deterrent compounds (Thacker *et al.*, 1997). In a laboratory study, rabbitfish fed preferentially on the red alga *Acanthophora spicifera* over *L. majuscula* containing LTA. However, when LTA was not detectable in *L. majuscula*, the fish consumed equal quantities of the cyanobacterium and red alga (Capper *et al.*, 2006c).

The mechanism by which animals detect LTA is not currently understood. Although it appears that fish are able to discriminate between chemically and non-chemically defended foods, the mechanisms by which fish detect and choose food are not clear. Rabbitfish have a high olfactory sensitivity to amino acids that stimulate feeding (Ishida and Kobayashi, 1992). They also appear to discriminate food on the basis of olfactory rather than gustatory sensitivity (Ishida and Kobayashi, 1992), but we know of no work that assesses how these fish detect deterrent secondary metabolites.

Animals that do not selectively forage on *L. majuscula* but consume it incidentally when it is growing on their normal food source may also be exposed to LTA. Green turtles (*Chelonia mydas*) in Shoalwater Bay, Australia, consumed only small amounts ($<1\%$ diet volume) of *L. majuscula* during a large bloom that covered extensive areas of

their normal seagrass forage (Arthur *et al.*, 2006a). Despite trying to avoid the cyanobacterium, they still consumed small amounts while feeding, and LTA has been detected in tissue samples collected from green turtles in Moreton Bay, Australia, where extensive blooms of *L. majuscula*, containing LTA, frequently occur on seagrass beds (Arthur *et al.*, 2007).

Studies on the physiological effects of LTA on animals likely to encounter *L. majuscula* in the wild are scarce. As previously discussed, specialist grazers are able to store and detoxify LTA with no apparent detrimental effects (Kato and Scheuer, 1975, 1976), but the impacts of incidental exposure to LTA on non-specialists are unclear. As was suggested for OA, incidental exposure to LTA in green turtles could be an associated cause of fibropapillomatosis (FP), a neoplastic disease that is characterized by cutaneous lesions and visceral masses (Landsberg *et al.*, 1999; Arthur *et al.*, 2006b). There is a geographical association between regions where regular blooms of *Lyngbya* sp. occur and areas of high FP prevalence in the local turtle population, but this association may be related to poor ecosystem health or food limitations rather than a toxicological effect (Arthur *et al.*, 2007).

Marine turtles appear to forage selectively (Bjorndal, 1980), but in general, information about their sensory capabilities—particularly the role of sensory biology in foraging behavior—is scarce. Although turtles are capable of selecting food by using both visual and olfactory cues, food choice is probably stimulated primarily by visual cues rather than chemosensory ones. In a study of captive leatherback hatchlings, both visual and chemical cues independently elicited increased biting behavior and orientation toward the cue (rheotaxis), but when cues were combined, turtles disregarded chemical cues in the current and oriented toward the food visually (Constantino and Salmon, 2003). The chemoreceptor organs in sea turtles are located in the nasopharyngeal duct that runs from the external nares on the front of the head to the internal nares on the palate (Scott, 1979). Turtles "smell" underwater by opening and closing their mouths and pumping water through the nasal cavity, over the chemoreceptor organs (Walker, 1959; Manton, 1979). No work has been undertaken using natural products to assess these mechanisms in large generalist herbivores such as green turtles. However, it appears likely that turtles can detect compounds produced by marine organisms and hence avoid unpalatable foods.

Although LTA has been identified from turtle tissue (Yasumoto, 1998; Arthur *et al.*, 2007), little is known about trophic transfer of LTA or other *Lyngbya* metabolites through marine food webs. Few animals selectively feed on *L. majuscula,* and there is little evidence for the presence of natural predators of specialist herbivores like *S. striatus,* which are known to sequester LTA (Capper *et al.*, 2005). Laboratory studies have demonstrated that wrasse and bream consumed *S. striatus* regardless of whether the sea hares had been fed diets containing other *L. majuscula*-derived compounds (malyngamides A and B), indicating that some diet-derived compounds may not deter predators from consuming the sea hares (Pennings *et al.*, 2001). Such experiments have not been conducted for LTA.

The low palatability of *L. majuscula* to generalist consumers potentially gives *L. majuscula* a competitive advantage over other benthic species in coastal environments, allowing this blooming, nitrogen-fixing cyanobacterium to grow uncontrolled when environmental conditions are favorable (Dennison *et al.*, 1999; Albert *et al.*, 2005; O'Neil and Dennison, 2005). Uncontrolled blooms of cyanobacteria may lead to shading and blanketing of benthic organisms, resulting in a phase shift to cyanobacteria in areas previously dominated by seagrass, algae, or corals (O'Neil and Dennison, 2005; Paul *et al.*, 2005). Blooms of *L. majuscula* have been documented to cause loss of seagrass (Stielow and Ballantine, 2003; O'Neil and Dennison, 2005), but it is not clear whether this die-off is a chemically mediated impact or whether it is due to prolonged shading from the large biomass of cyanobacteria. Similar community changes may also be impacting reef communities. A study of the recruitment of coral larvae in Guam found that the presence of *L. majuscula* significantly reduced larval survival in *Acropora surculosa* and recruitment in *Pocillopora damicornis* (Kuffner and Paul, 2004). Similar studies in the Florida Keys showed that larvae of *Porites astreoides* avoided settling near *Lyngbya polychroa* and *Lyngbya confervoides* on recruitment tiles and that *L. majuscula* negatively impacted survival and recruitment of larvae of the octocoral *Briareum asbestinum* (Kuffner *et al.*, 2006). These studies highlight the potential for secondary metabolites to influence the structure of marine ecosystems, and demonstrate the lack of knowledge surrounding the allelopathic role of LTA and other cyanobacterial secondary metabolites.

Caulerpenyne

Chemically rich macroalgae can also become abundant under certain circumstances and lead to changes in community composition. Among the best examples are the invasive species of the green algae *Caulerpa*, particularly the pantropical *C. taxifolia*, which has invaded coastal areas of the northwestern Mediterranean. Since first detected near Monaco, it has spread extensively, in some cases hundreds of kilometers away from the site of its accidental introduction (Meinesz and Hesse, 1991; Meinesz *et al.*, 1993, 2001); however, Jaubert *et al.* (2003) provide evidence that the extent of the spread has been overestimated. Invasive *C. taxifolia* has also been discovered on the California coast (Jousson *et al.*, 2000). *Caulerpa* spp. are found worldwide, generally in shallow tropical and subtropical marine habi-

tats. These noncalcified algae can be found in abundance, sometimes in areas of significant herbivore populations. The algae grow vegetatively and can cover extensive areas.

Species of *Caulerpa* were among the first green algae that were investigated by natural product chemists. Australian workers studying *Caulerpa* species from southern Australia found various terpenes such as caulerpol, flexilin, and trifarin (Blackman and Wells, 1976, 1978). Caulerpenyne, a unique acetylenic sesquiterpenoid that is closely related to flexilin, was first isolated from a Mediterranean collection of *C. prolifera* (Amico *et al.*, 1978), but has since been found as the major metabolite in many other *Caulerpa* spp. (Fig. 2). These *Caulerpa* compounds were the first natural products isolated that possessed the bis-enol acetate functional group, which is a common feature among green algae of the genera *Caulerpa*, *Udotea*, *Halimeda,* and related green algae. This functional group represents an acetylated dialdehyde group to which high biological activity is generally attributed (Paul and Fenical, 1986).

Several monocyclic sesquiterpenes have been reported from species of *Caulerpa*, including *C. bikinensis* from Palau (Paul and Fenical, 1982), *C. flexilis* var. *muelleri* from Western Australia (Capon *et al.*, 1981), and *C. ashmeadii* from the Florida Keys (Paul *et al.*, 1987). Major compounds usually contain the same bis-enol acetate group found in caulerpenyne and other linear terpenes from *Caulerpa* and related green algae. In addition, minor acetoxy-aldehydes and dialdehydes have been reported from these algae. When compared to the bis-enol acetates, the aldehydes from *C. ashmeadii* and *C. bikinensis* were more toxic to fish (Paul and Fenical, 1982; Paul *et al.*, 1987).

Caulerpenyne is also the major terpene produced by the Mediterranean populations of *C. taxifolia* (Guerriero *et al.*, 1992, 1993; Dumay *et al.*, 2002). Although this alga has been reported to contain higher levels of caulerpenyne than other species of *Caulerpa* (Guerriero *et al.*, 1992; Amade and Lemee, 1998; Dumay *et al.*, 2002), this is not always the case (Jung *et al.*, 2002). Tropical species of *Caulerpa* are highly variable in their production of caulerpenyne and, for example, concentrations of this compound in *C. sertularioides* from Guam are higher than those reported for the Mediterranean alga (Meyer and Paul, 1992).

In biosynthetic labeling studies, Pohnert and Jung (2003) administered precursors, including 1-^{13}C acetate and $^{13}CO_2$, labeled with stable isotopes to *Caulerpa taxifolia* growing in artificial seawater. The precursors were incorporated into caulerpenyne with a significant degree of labeling, which made it possible to deduce early stages of terpene biosynthesis in the alga. From the labeling pattern, the authors concluded that the sesquiterpene backbone is biosynthesized *via* the methyl-erythritol-4-phosphate (MEP) pathway, which occurs in the chloroplasts where CO_2 is fixed by photosynthesis. However, formation of the acetyl groups in caulerpenyne relies on cytoplasm-derived acetate (Pohnert and Jung, 2003).

Mediterranean species of *Caulerpa* transform caulerpenyne to oxytoxins 1 and 2 and related acetoxy aldehydes by a wound-activated process that results from deacetylation of caulerpenyne (Jung and Pohnert, 2001; Jung *et al.*, 2002) (Fig. 2). Because of their aldehyde functional groups, the oxytoxins are probably more potent chemical defenses than caulerpenyne, although this has not been directly tested because of their instability. A similar wound-activated transformation has been reported for green algae of the genus *Halimeda* (Paul and Van Alstyne, 1992). In many species of *Halimeda*, the diterpene bis-enol acetate halimedatetraacetate is converted to the aldehyde halimedatrial when algae are crushed or injured. Halimedatrial is a more potent toxin and feeding deterrent than its precursor halimedatetraacetate (Paul and Van Alstyne, 1992). Activated chemical defenses may be common among green algae of the families Caulerpaceae and Udoteaceae.

Caulerpenyne shows diverse biological activities. Extracts of *Caulerpa* spp. and caulerpenyne have been reported to show antimicrobial (Hodgson, 1984; Paul and Fenical, 1986; Smyrniotopoulos *et al.*, 2003; Freile-Pelegrín and Morales, 2004) and antiproliferative (Hodgson, 1984; Fischel *et al.*, 1995; Cavas *et al.*, 2006) activities. Caulerpenyne blocked cleavage of developing sea urchin eggs (Paul and Fenical, 1986; Pesando *et al.*, 1996), most likely because it inhibits microtubule polymerization (Barbier *et al.*, 2001) and can induce apoptosis in mammalian (neuroblastoma) cells (Cavas *et al.*, 2006). Allelopathic activities have also been reported for extracts of *Caulerpa* spp. and caulerpenyne toward microalgae (Lemee *et al.*, 1997; Smyrniotopoulos *et al.*, 2003) and the fouling polychaete worm *Hydroides elegans* (Dobretsov *et al.*, 2006).

Caulerpenyne also shows neurological activity. Caulerpenyne affected neurons in invertebrate model organisms (leeches) by modifying the electrophysiological properties of touch mechanosensory cells. Caulerpenyne depresses afterhyperpolarization in the cells primarily by inhibiting the Na^+/K^+-ATPase in these neurons (Mozzachiodi *et al.*, 2001). The authors of this study suggested that these electrophysiological effects on neurons might explain an incident of human poisoning that included neurological symptoms of amnesia, vertigo, and hallucinations after the fish *Sarpa salpa*, which eats *C. taxifolia,* was consumed (De Haro *et al.*, 1993). These findings may have implications for the neuroecological effects of caulerpenyne on other marine consumers.

A recent study of the invasive *C. taxifolia* in the Mediterranean examined the role of caulerpenyne in wound healing in the alga (Adolph *et al.*, 2005). After an injury, an esterase rapidly transforms caulerpenyne to oxytoxin 2 (Jung and Pohnert, 2001; Jung *et al.*, 2002), and the resulting 1,4-dialdehyde is highly reactive and cannot even be

detected 4 min later (Adolph *et al.*, 2005). The decay kinetics of oxytoxin 2 matched those of the formation of the external wound plug of *C. taxifolia*. Adolph *et al.* (2005) proposed that proteins cross-linking with oxytoxins and similar reactive aldehydes in *C. taxifolia* are essential for wound-plug formation. This suggests another function for caulerpenyne in addition to its antimicrobial, neurological, and feeding deterrent activities.

In the tropics, most species of *Caulerpa* are readily consumed by herbivorous reef fish such as rabbitfish (Siganidae) and surgeonfish (Acanthuridae) (Paul and Hay, 1986; Paul *et al.*, 1990), although some species, such as *C. prolifera*, are less palatable than others (Paul and Hay, 1986). Neither crude extracts of several species of *Caulerpa* nor the purified terpene caulerpenyne deterred feeding by any species of herbivorous fish they have been tested against (Paul *et al.*, 1987, 1990; Meyer and Paul, 1992; Paul and Van Alstyne, 1992; Meyer *et al.*, 1994). Tropical invertebrate generalist herbivores, such as sea urchins, can be deterred by caulerpenyne even though tropical herbivorous fish usually are not. In one of the first studies to examine the chemical defenses of marine algal natural products, McConnell *et al.* (1982) showed that caulerpenyne deterred feeding by the sea urchin *Lytechinus variegatus*. Erickson *et al.* (2006) demonstrated that the subtropical sea urchin *Echinometra lucunter* was deterred by relatively high concentrations of caulerpenyne (4% dry mass).

Some sacoglossan opisthobranch molluscs specialize on *Caulerpa* spp. and sequester chemical defenses from their host algae (Gavagnin *et al.*, 1994, 2000; Cimino and Ghiselin, 1998; Marin and Ros, 2004). Species of *Elysia*, *Oxynoe*, *Volvatella*, and *Lobiger* feed suctorially on various species of *Caulerpa* (Jensen, 1983). Caulerpenyne is present in some species of *Elysia* (Gavagnin *et al.*, 2000), and it is modified into oxytoxins 1 and 2 by species of *Oxynoe* and *Lobiger* and some species of *Elysia* (Gavagnin *et al.*, 1994, 2000; Marin and Ros, 2004) (Fig. 2). These compounds are also present in mucous secretions of the animals, where they are thought to function as chemical defenses (Marin and Ros, 2004). *Oxynoe olivacea* contains hydrolytic enzymes that convert caulerpenyne to the oxytoxins (Cutignano *et al.*, 2004). While it has been suggested that these specialist consumers of *Caulerpa* spp. might be used for biocontrol (Thibaut *et al.*, 2001), it is unlikely that sacoglossan molluscs could achieve the population densities necessary to control invasive blooms.

Caulerpa taxifolia is unpalatable to generalist herbivores in the Mediterranean (Boudouresque *et al.*, 1996), and can affect the physiology of sympatric fish by altering enzymatic detoxification systems in their livers (Uchimura *et al.*, 1999). It is likely that the terpenes function as chemical defenses against these non-adapted herbivores; however, caulerpenyne has not been directly tested against Mediterranean herbivores. It has been hypothesized that the chemical defenses of *C. taxifolia* may have facilitated its biological invasion into Mediterranean waters, where it reduces biodiversity, thus negatively affecting the benthic community structure in areas where it occurs (Francour *et al.*, 1995; Bellan-Santini *et al.*, 1996). Davis *et al.* (2005) reached similar conclusions for invasive *Caulerpa* spp. in Southeastern Australia, because fish and invertebrate herbivores largely avoided these algae and their extracts in feeding trials.

Marine Invertebrates: Bryostatins and Isocyano Terpenes

Marine invertebrates, especially sponges, ascidians, and bryozoans, are prolific sources of novel, diverse bioactive compounds (Faulkner, 2002; Blunt *et al.*, 2003). As more has been discovered about the global and taxonomic distribution of bioactive compounds in terrestrial and marine organisms, and because some compounds are structurally similar to known microbial metabolites, many natural products isolated from invertebrates are thought to be synthesized by symbiotic microorganisms (Kobayashi and Ishibashi, 1993; Piel, 2004). However, a bacterial origin of marine natural products has been demonstrated in very few cases (reviewed in Piel, 2006), due to the complexity of naturally occurring microbial assemblages in most marine invertebrates. Unlike one-host/one-symbiont associations, such as the well-described squid-bacteria (*Euprymna scolopes-Vibrio fischeri)* symbiosis, sponges, ascidians, and bryozoans harbor abundant, diverse bacterial and archaeal assemblages, presenting a significant obstacle to identifying species-specific associations. Recent research indicates that sponges have evolved to maintain long-term species-specific symbioses with diverse groups of bacteria *via* intergenerational (vertical) transmission (Schmitt *et al.*, 2007; Sharp *et al.*, 2007; reviewed in Taylor *et al.*, 2007).

Though most obligate symbiotic bacteria and archaea have eluded cultivation attempts, combined methodologies from microbial ecology, molecular genetics, genomics, and natural products chemistry have laid a valuable foundation for work on biosynthetic origin studies, allowing the symbiotic sources of a handful of marine natural products to be identified (Hildebrand *et al.*, 2004b). Bacterial and archaeal genomes are relatively small compared to those of their animal hosts, and their biosynthetic pathways tend to be organized in contiguous DNA sequence, facilitating cloning and expression. As a result, molecular approaches to clone and express biosynthetic genes from symbionts have become of great interest as a way to overcome the problem of natural levels of supply (Hildebrand *et al.*, 2004b; Piel, 2006).

Bryostatins

Despite the challenges of identifying symbiotic sources of natural products, there are some symbioses in which bioactive compound production and the ecological implications of the compound are well understood. For the bryozoan *Bugula neritina,* there is conclusive evidence that a symbiotic bacterium produces a chemical defense compound for its host. The symbiotic bacterium in *B. neritina* has been identified, and a putative bryostatin biosynthetic gene cluster has been sequenced from the symbiont genome. Biomedical investigations have revealed the mechanism of action responsible for cytotoxicity of the bryostatins, and the ecological implications of this specific symbiosis include the protection of the host, particularly the larval and early life stages.

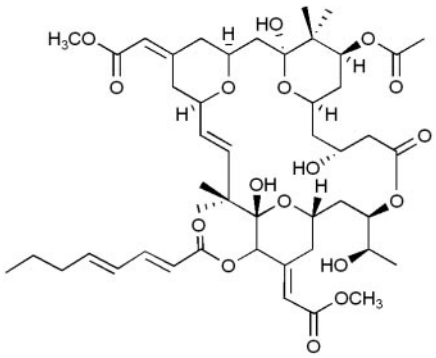
Bugula neritina, a temperate intertidal bryozoan that often extensively fouls docks and boat hulls across the globe, forms chitinous, upright, branching colonies (Woollacott and Zimmer, 1977). The lophophore, or feeding tentacles, of the soft-bodied feeding animal can retract into the chitinous cuticle in response to physical or chemical disturbance (Woollacott and Zimmer, 1977), but *B. neritina* lacks the mechanical defense of specialized zooids called avicularia and vibracula, which are present in many other bryozoan species. The bryostatins (Fig. 3), a group of compounds with significant anti-cancer activity, were isolated from *B. neritina* (Pettit *et al.*, 1982; Pettit, 1991). As complex polyketides, the bryostatins were long suspected, along with natural products from several other bryozoan species, to be produced by symbiotic bacteria (Anthoni *et al.*, 1990). The putative biosynthetic gene cluster *bry*, which consists of five modular polyketide synthase (PKS) genes, has been identified (Sudek *et al.*, 2007). A region coding for a keto synthase domain of the first open reading frame, *bryA*, is expressed in *"E. sertula"* in *B. neritina* larvae (Davidson *et al.*, 2001; Hildebrand *et al.*, 2004a).

Bryostatins have potent anti-tumor activity, so their cellular mechanism of action is relatively well researched. Extensive clinical research has established that bryostatin 1 (Fig. 3) competes for the same binding site as phorbol esters on mammalian protein kinase C (PKC) (Wender *et al.*, 1988; Kazanietz *et al.*, 1994). The binding ability for PKC is significantly higher in bryostatins than in the tumor-promoting plant phorbol esters (de Vries *et al.*, 1988). The capability of bryostatins to displace phorbols irreversibly (de Vries *et al.*, 1988) is the basis of the phorbol dibutyrate (PDBu) displacement assay, which has been used at the National Cancer Institute to screen crude extracts from marine organisms and to assess the presence of bryostatins in *B. neritina* samples (de Vries *et al.*, 1988, 1997; Schaufelberger *et al.*, 1990). Unlike phorbol esters, the bryostatins apparently do not play a role in tumor metastasis, but they competitively bind PKC and stimulate kinase activity *in vivo* (Berkow *et al.*, 1993), making them potent tumor-fighting compounds. It is not yet known, however, whether the interactions of bryostatins with PKC are involved in their ecological activity.

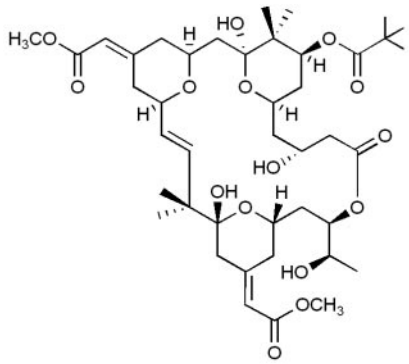
Bioactive compounds in invertebrates impact larval morphology and behavior by making the larvae unpalatable to predators or by preventing microbial fouling (Lindquist *et al.*, 1992; Lindquist and Hay, 1995, 1996; Lindquist, 1996; McClintock and Baker, 1997; Iyengar and Harvell, 2001). A single species of symbiotic gamma-proteobacterium, identified as "*Candidatus* Endobugula sertula," was shown to reside in the pallial sinus of *B. neritina* larvae (Haygood and Davidson, 1997). Transmission electron microscopy demonstrated the presence of bacteria in larval pallial sinus and the funicular cords, channels of tissue that interconnect zooids, in adult *B. neritina* colonies (Woollacott and Zimmer, 1975; Woollacott, 1981), and bacteria in the *B. neritina* funicular system have since been identified as "*E. sertula*" with sequence-specific probes (Sharp *et al.*, in press). At least three cryptic species of *B. neritina* occur in the United States, and each exhibits different bryostatin profiles and possesses phylogenetically distinct but closely related symbionts (Davidson and Haygood, 1999; McGovern and Hellberg, 2003). In addition, a population of *B. neritina* that appears to be aposymbiotic and lacking bryostatins was identified off the coast of Delaware (McGovern and Hellberg, 2003; Lopanik *et al.*, 2004).

Larvae harvested from antibiotic-treated adult *B. neritina* colonies have significantly decreased bryostatin levels (Davidson *et al.*, 2001; Lopanik *et al.*, 2004), and bryostatins isolated from *B. neritina* are responsible for the fish-feeding deterrence previously observed in feeding assays (Lindquist and Hay, 1996; Lopanik *et al.*, 2004), indicating that symbiont-derived bryostatins chemically defend the host larvae. The growth, settlement, and metamorphosis of antibiotic-treated *B. neritina* do not appear to be significantly altered (Davidson *et al.*, 2001; Lopanik *et al.*, 2004), suggesting that the symbionts are not involved in host nutrition or development; rather, the symbionts produce the bryostatins for chemical protection of the host. Fish-feeding assays suggest that bryostatin 10 (Fig. 3) is one of the most abundant bryostatins in *B. neritina* larvae, perhaps responsible for the ecological activity. Localization of the bryostatins using PKC-based immunohistochemistry demonstrated that the bryostatins are loaded onto larvae before their release from adults, and this protective coating of bryostatins remains around the exterior of *B. neritina* individuals after settlement and throughout metamorphosis until the chitinous cuticle develops (Sharp *et al.*, in press).

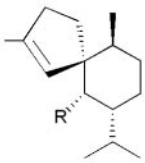
Bugula simplex possesses closely related bacterial symbionts falling into the genus "*Endobugula*" (Lim and Haygood, 2004). It is unknown which environmental factors have selected for the variable presence of symbionts and chemical defense production across the genus *Bugula*.



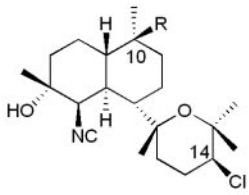
bryostatin 1



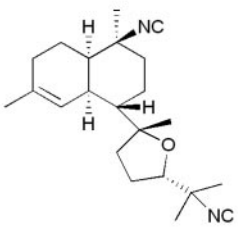
bryostatin 10



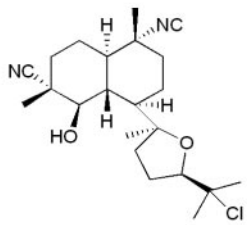
axisonitrile-3 R=NC
axisothiocyanate-3 R=NCS
axamide-3 R=NHCHO



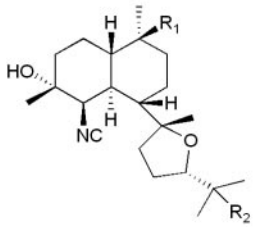
kalihinol A R=NC
kalihinol X R=NCS; epimer at C10



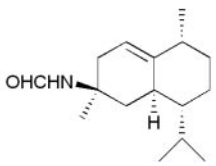
kalihinene



isokalihinol B



	R_1	R_2
kalihinol F	NC	NC
kalihinol G	NC	NCS
15-formamido-kalihinol F	NC	NHCHO



(3*S**, 5*R**, 6*R**,9*R**)-3-formamido-1(10)-cadinene

Figure 3. Structures of compounds in marine invertebrates.

There is a wide range of pigmentation and size in larvae of different *Bugula* species. *B. neritina* and *B. simplex* are relatively large and conspicuous compared to aposymbiotic, non-defended species such as *B. turrita* (Lim and Haygood, 2004). As *B. neritina* is a relatively dominant fouling organism and cosmopolitan in distribution, it is tempting to

hypothesize that the bryostatins confer competitive advantage to *B. neritina* by protecting larvae throughout the larval swimming and metamorphosis stages, preventing settlement of other invertebrate larvae or predation.

Recent studies using a mouse model system demonstrated that bryostatin 1 (Fig. 3) has the potential to counter the effects of depression and dementia, making it a promising therapeutic agent for Alzheimer's disease and other central nervous system disorders in humans (Sun and Alkon, 2005, 2006; Alkon *et al.*, 2007). PKC activation by low concentrations of bryostatins has been shown to enhance long-term memory in the nudibranch *Hermissenda* (Alkon *et al.*, 2005; Kuzirian *et al.*, 2006). Although clinical testing has revealed that the interactions of bryostatins with PKC can mediate processes in animals ranging from inhibition of cell growth to activation of neurological processes, further work is necessary to determine the biochemical mechanisms by which bryostatins deter predators. This new neurological aspect of the bioactivity of the bryostatins could lay the foundation for future investigations of their effects on sensory processes and feeding behavior in ecologically relevant predators.

The dorid nudibranch *Polycera atra*, which is cryptic on *Bugula neritina* colonies, feeds on and lays conspicuous white egg masses on *B. neritina* colonies. *P. atra* feeds on colony tips and swimming larvae (pers. comm., C. Sheehan, Scripps Institution of Oceanography), both of which have high concentrations of bryostatins (Davidson, 1999; Davidson *et al.*, 2001; Lopanik *et al.*, 2004). Mass spectrometry and PDBu assays with *P. atra* extracts indicate that, like many other dorid nudibranchs, *P. atra* sequesters bioactive compounds from the diet (Davidson, 1999), sometimes in levels higher than those found in adult *B. neritina* colonies. Conversely, PDBu assays indicate that *P. atra* individuals kept in tanks without *B. neritina* for 36 hours possess bryostatins in lower concentrations, comparable to those in adult *B. neritina* colonies (Davidson, 1999). Egg cases laid during the starvation period, however, have high concentrations of bryostatins, indicating that the bryostatin levels in individual *Polycera* nudibranchs depend on their egg-laying and feeding history (Davidson, 1999). Clearly, bryostatins have influenced the evolution of highly integrated relationships between the symbiont "*E. sertula*," the chemically defended *B. neritina*, and its nudibranch predator *P. atra*, which then uses that chemical defense for its conspicuous egg masses.

Isocyano terpenes

Marine chemical defenses from sponges have also received considerable attention, including the isocyano terpenes, which are most commonly found in Halichondridae sponges. The first marine isocyano terpene was isolated in 1973 (Cafieri *et al.*, 1973) from the sponge *Axinella cannabina*. Since then more than 150 isocyano terpenes have been structurally characterized; these are predominantly sesquiterpenes and diterpenes with at least one nitrogen that forms a cyanide functional group. The diversity of marine isocyano terpene structures has been reviewed (Edenborough and Herbert, 1988; Chang and Scheuer, 1993; Chang, 2000; Garson and Simpson, 2004), and here we briefly also discuss the structurally related isothiocyanates and formamides. Isocyano terpenes are found in a variety of organisms, including fungi, bacteria, cyanobacteria, sponges, and nudibranchs; however, for the purpose of this review, we focus on the compounds isolated from marine sponges and nudibranchs. Links from the cellular mechanisms of action of the marine isocyano terpenes to ecological function remain to be tested, but preliminary evidence suggests they are important in the interactions of sponges and their predators.

During the last 20 years, multiple reviews of the biosynthesis of isocyano terpenes and related compounds have been published (Edenborough and Herbert, 1988; Scheuer, 1992; Garson and Simpson, 2004). Because of their structural similarity to tyrosine, most terrestrial isocyano terpenes are thought to be derived from amino acids; however, the marine isocyano terpenes are not structurally similar to amino acids, suggesting a different biosynthetic pathway. Early work in Australia and Hawaii showed that sponges can incorporate the inorganic cyanide functional group into sesquiterpene and diterpene skeletons (Garson, 1986; Karuso and Scheuer, 1989). Further studies on the biosynthesis of isocyanide compounds from inorganic cyanide precursors by the sponges *Amphimedon terpenensis*, *Acanthella cavernosa*, *Axinyssa* n. sp., and *Stylotella aurantium* are reviewed by Garson and Simpson (2004).

Diverse sponges within the family Halichondridae contain isocyano terpenes, but little work has been done to determine whether it is the sponges or their associated bacteria that are making these compounds. Through Ficoll density-gradient fractionation and centrifugation, sponge cells were separated from their associated bacteria, and isocyano terpenes were localized to sponge cell membranes in *Amphimedon terpenensis* (Garson *et al.*, 1992). Though bioactive compounds have been localized on the cellular level in several sponges (Unson *et al.*, 1994; Flowers *et al.*, 1998; Gillor *et al.*, 2000; Salomon *et al.*, 2001), localization may simply indicate the site where a compound is needed, rather than the site of origin (reviewed in Hildebrand *et al.*, 2004b; and König *et al.*, 2006). Molecular biology and metagenomics techniques based on identification of biosynthetic gene clusters have laid a foundation for future work to determine the source of bioactive compounds in many marine invertebrates (Davidson *et al.*, 2001; Piel *et al.*, 2004, 2005; Flatt *et al.*, 2005; Schmidt, 2005; Schmidt *et al.*, 2005). Similar approaches focusing on isocyano terpene biosynthesis are critical for determining the source of the

isocyano terpenes in sponges. Most of the biosynthetic studies have shown that sponges can incorporate cyanide into a terpene skeleton, but the origin of the cyanide and how the sponges prevent autotoxicity are unknown.

The biochemical mechanism of action of isocyano terpenes has been identified in various clinical tests, but the ecological consequences of the bioactive compounds remain unclear. Cyanide, which is a potent inhibitor of many redox-based enzymes, including cytochrome oxidase, a principal component of the electron transfer chain (Solomonson, 1981), inhibits respiration and is therefore a potent cytotoxin. The diterpenes kalihinol A and kalihinol F (Fig. 3), isolated from the sponge *Acanthella cavernosa*, inhibited the growth of the bacteria *Bacillus subtilis*, *Staphylococcus aureus*, and *Candida albicans* (Chang *et al.*, 1984; Patra *et al.*, 1984). The formide (3*S**,5*R**,6*R**,9*R**)-3-formamido-1(10)-cadinene isolated from a Palauan collection of the sponge *Axinyssa aplysinoides* also inhibited the growth of *S. aureus* and *B. subtilis* (Compagnone and Faulkner, 1995). In addition to growth inhibition of some microbes, the diterpene isocyanides kalihinene and isokalihinol B (Fig. 3) from the sponge *Acanthella klethra* exhibited antifungal activity against *Mortierella ramannianus* and *Penicillium chrysogenum* (Fusetani *et al.*, 1990b). Some isocyanide compounds are also toxic to parasites, and their effect on the malaria parasite *Plasmodium falciparum* is the best studied (Angerhofer and Pezzuto, 1992; König *et al.*, 1996; Wright *et al.*, 1996, 2001; Simpson *et al.*, 1997).

Even though many of these compounds have been tested against common laboratory microbes, little work has been done to understand the cellular mechanisms by which the isocyano terpenes inhibit bacterial growth. One recent paper demonstrated that the diterpene kalihinols inhibited bacterial biosynthesis of folate (Bugni *et al.*, 2004), resulting in the disruption of a wide range of bacterial primary metabolic processes. In a novel bioassay in which β-galactosidase activity is upregulated in *Escherichia coli* when folate biosynthesis is inhibited, Bugni *et al.* (2004) demonstrated that some kalihinols (Y, X, F, G), kalihinene, and 15-formamido-kalihinol F inhibited bacterial folate biosynthesis (Fig. 3). Kalihinol A (Fig. 3) had only slight activity in these assays, suggesting that the substitution at C-10 greatly changes the bioactivity of these diterpenes.

Perhaps the best-studied ecological role for marine isocyanides is the inhibition of biofouling. The most common assay for biofouling is inhibition of the settlement and metamorphosis of the barnacle *Balanus amphitrite* (Rittschof *et al.*, 1992). *Balanus* spp. often settle on the hulls of ships and are widely distributed in the ocean. Their larvae are easily maintained in the laboratory, making them convenient for use in determining potential antifouling activity. Both sesquiterpenes and diterpenes from the sponge *Acanthella cavernosa* inhibited settlement and metamorphosis of *B. amphitrite* but exhibited low toxicity (Okino *et al.*, 1995, 1996; Fusetani *et al.*, 1996). Kitano *et al.* (2004) synthesized 10 novel isocyanocyclohexane compounds to test structure-activity relationships and found that the derivatives with an ester functional group reduced settlement and metamorphosis, but the ether derivatives did not. Compounds without the cyanide functional group did not inhibit barnacle settlement. Antifouling isocyanide compounds were found in halichondrid sponges and some phyllidiid nudibranchs (Fusetani, 2004). Although many isocyanide terpenes show antifouling activity against *B. amphitrite* (reviewed in Fusetani, 2004), no studies have examined the neurological response of larvae to these compounds or whether isocyanides also inhibit the formation of biofilms. Isocyano terpenes should be tested, using field methods (Dobretsov *et al.*, 2004), against natural biofouling organisms to determine whether these compounds inhibit biofilm formation or are just active against *B. amphitrite* larvae.

Isocyanide terpenes are found in a variety of sponges and nudibranchs, but little is known about the toxicity of these compounds to ecologically relevant species. The mucus of the nudibranch *Phyllidia varicosa* was toxic to a variety of crustaceans and a fish, but had no apparent effect on the nudibranch *Placobranchus ianthobapsus* and the crab *Metapograpsus messor*, although these experiments were not replicated (Johannes, 1963). Even though Johannes used species that co-occur with these nudibranchs, it is impossible to know the chemical composition of the mucus he used. Phyllidiid nudibranch extracts (which often contain isocyano terpenes derived from their sponge diets) were toxic against common bacteria, fungi, and the mosquitofish *Gambusia affinus* (Gunthorpe and Cameron, 1987). The isolated isocyano terpene, 2-isocyanoallopupukeanane, was tested for its toxicity against the killifish *Oryzias latipes* and was found to have an LC_{50} of 10 μg/ml (Fusetani *et al.*, 1991). Many laboratory organisms such as mosquitofish and killifish are not encountered in the same habitat as the sponges and nudibranchs that contain isocyanide compounds, and therefore experiments using these organisms can only suggest a likely ecological function.

Sponges and nudibranchs are benthic organisms that often use chemical defenses to avoid being eaten by a variety of predators. Surprisingly few ecologically relevant experiments have shown that isocyano terpenes deter feeding by ecologically relevant predators. Preliminary field experiments with an Australian collection of *Acanthella cavernosa* showed that both the crude extract and the fraction that contained sesquiterpenes deterred fish feeding, but the pure compound axisonitrile-3 did not (Garson *et al.*, 2000) (Fig. 3). Crude extracts of the sponge *Acanthella cavernosa* from Guam, which contained isocyano terpenes, reduced feeding by two natural assemblages of reef fish (Ritson-Williams and Paul, 2007). These extracts were potent deterrents and significantly reduced feeding at 1% dry weight and at 0.2% dry weight at two reefs with different assemblages of reef

fish (natural concentration of the crude extract in *A. cavernosa* was 2.9% dry weight); however, the compounds responsible for feeding deterrence were not isolated.

Some specialist predators, such as nudibranchs, are capable of sequestering isocyanide compounds from their sponge diets (Burgoyne *et al.*, 1993; Cimino and Sodano, 1994). Phyllidiid nudibranchs can be brightly colored (aposematic coloration), and many of them contain isocyanide compounds (Fusetani *et al.*, 1990a, 1991), often the same isocyano terpenes as their prey sponges, suggesting a trophic transfer of these compounds (Chang and Scheuer, 1993; Avila, 1995; Garson *et al.*, 2000). On Guam, *Phyllidiella granulatus* was observed feeding on the sponge *Acanthella cavernosa*, and both the nudibranch and its mucus contained the same isocyano diterpenes as the sponge (Ritson-Williams and Paul, 2007). The best evidence for sequestration of isocyano terpenes by a nudibranch is a study by Dumdei *et al.* (1997), in which the investigators radiolabeled axisonitrile-3 and axisothiocyanate-3 (Fig. 3) in *A. cavernosa* from Australia and showed that the labeled compounds were present in *Phyllidiella pustulosa* after the nudibranchs fed on the sponge.

Nudibranch evolution is thought to be closely tied to the use of chemical defenses because nudibranchs have lost the physical defense of a shell (Faulkner and Ghiselin, 1983). Surprisingly, the compounds found in phyllidiid nudibranchs have rarely been tested as fish feeding deterrents even though these opisthobranchs are conspicuously colored and are diurnal. Crude extracts of the phyllidiid nudibranchs *Phyllidia varicosa, Phyllidiella elegans*, and *Phyllidiella pustulosa* reduced fish feeding in Guam at natural concentrations (Ritson-Williams and Paul, 2007). Interestingly, *P. pustulosa* was collected from both Guam and Palau, and only the crude extract from the Palauan population deterred feeding by fish from Guam. Unfortunately, the sponges that *P. pustulosa* was feeding on were not found on either island. These experiments used the crude extracts of multiple individual nudibranchs pooled together, and future research should focus on testing isolated isocyano terpenes to determine if they are responsible for the observed ecological activity.

Consumer Neuroecology

Many of the compounds discussed in this review have been studied for the purpose of identifying their actual source and to understand their biosynthesis, mechanisms of action, and ecology, but the effects of bioactive compounds on the neuroecology and behavior of specialist and generalist consumers are rarely investigated. Some marine natural products have been studied for their toxicity to nervous systems, but few of these investigations have determined how marine consumers sense and respond to these natural products (Derby, 2007). Even less understood is how these natural products affect a consumer's ability to learn and remember in predator-prey interactions (Lindquist and Hay, 1995; Long and Hay, 2006), and ultimately how resultant behavioral changes can impact the ecology of the organism. To stimulate further research on these topics, in this section we provide neuroecological examples that relate to the natural products we have discussed.

Tight associations have evolved between specialists and their prey, and many natural products mediate different types of behavior in specialist consumers. Squid, nudibranchs, sea hares, and crustaceans have been used to study the basic construction of the simple nervous system of marine invertebrates and the types of behavior that neurons regulate (Sattelle and Buckingham, 2006). Many of the algae and invertebrates in this review have specialist opisthobranch consumers that contain the same secondary metabolites as their prey—for example, *Elysia* spp.-*Caulerpa* spp., *Stylocheilus striatus-Lyngbya majuscula*, *Polycera atra-Bugula neritina*, phyllidiid nudibranchs-halichondrid sponges—but how these specialists detect ecologically relevant natural products is still unknown. In contrast, generalist herbivores, which are often deterred by secondary metabolites, provide an opportunity to understand how predators detect and avoid diverse compounds.

Marine gastropods are often used as a model system for neurobiology research (Chase, 2002). The gastropod nervous system is relatively simple, and much of the research on gastropods has focused on which ganglion drives which behavioral process (*e.g.,* locomotion, feeding, reproduction, and defense). Marine gastropods are known to use chemoreception and mechanoreception to sense their environment, and some gastropods also have nociception receptors, which detect physical and chemical danger cues and elicit a defensive reaction (Chase, 2002). Even though these receptors are found in marine gastropods such as *Aplysia* spp., their function in response to natural toxins has not been determined. Chemoreception has not been studied in any of the specialist opisthobranchs mentioned in this review. How these opisthobranchs select their prey and whether they avoid other chemical defenses have rarely been investigated.

The specialist nudibranch *Tritonia diomedea* used water-soluble cues in flow to move toward its prey and toward conspecifics in laboratory experiments (Wyeth and Willows, 2006b). In Y-maze experiments, *T. diomedea* consistently moved toward chemical cues, but the chemotaxis response was eliminated with the removal of rhinophores, the major olfactory organ in opisthobranchs (Chase, 2002). Using an *en passant* suction electrode to measure action potentials from neurons in rhinophores isolated from *T. diomedea*, Wyeth and Willows (2006b) detected significant increases in the number and frequency of action potentials associated with waterborne cues from prey, predator, and conspecific individuals. These experiments also indicated

that physical properties such as flow affect the ability of *T. diomedea* to use olfaction to detect prey and conspecifics in the laboratory (Wyeth and Willows, 2006b), and video analysis demonstrated that water flow affects chemotaxis similarly in the field (Wyeth and Willows, 2006a). An important component of understanding this specialist behavioral response will be the structural elucidation of compounds that interact with the neurological receptors in *T. diomedea*. Future studies with neurological methods similar to those described above for *T. diomedea* could be used to characterize the neurological responses of specialist opisthobranch predators to the natural products found in their prey.

In addition to attracting adult predators and stimulating their feeding, bioactive compounds can mediate species-specific larval settlement and metamorphosis. Opisthobranchs typically have complex life histories, including a planktonic larval stage that allows dispersal. Because many marine invertebrates have evolved to rely on specific prey species, habitat selection during the larval stage is often critical for their survival (Pawlik, 1992; Hadfield and Paul, 2001). Upon settlement, larvae undergo metamorphosis, a series of morphological and physiological processes directed by neurotransmitters in the larval tissues. Relatively few natural settlement cues have been structurally characterized, owing to their low concentrations and the challenges of isolating them from seawater. One of the few ecologically relevant settlement cues that have been isolated for marine invertebrates is histamine, which induces metamorphosis in the sea urchin *Holopneustes purpurascens* (Swanson *et al.*, 2004) and is a ubiquitous neuralsignaling molecule in many organisms. Molecules found on the benthos that are similar to neurotransmitters such as GABA and L-dopa can act as settlement inducers for molluscan larvae (Morse *et al.*, 1979; Coon *et al.*, 1985; Morse, 1985).

Studies of metamorphosis in the aeolid nudibranch *Phestilla sibogae*, known to specialize on multiple species of coral in the genus *Porites* (Ritson-Williams *et al.*, 2003), demonstrated that the larvae metamorphose only in response to an unidentified waterborne cue released by these corals (Hadfield and Scheuer, 1985). The cue initiates a cell signaling cascade in the apical sensory organ (thought to be the major sensory organ of the larvae) that induces metamorphosis from a veliger to a juvenile slug (Pires and Hadfield, 1993; Hadfield *et al.*, 2000). *Phestilla sibogae* larvae use common neurotransmitters, including catecholamines and epinephrine, during the process of metamorphosis (Hadfield, 1984; Kempf *et al.*, 1992; Hadfield *et al.*, 2000; Pires *et al.*, 2000). Natural chemical cues from *Porites compressa* not only initiate metamorphosis but also mediate veliger swimming behavior (Hadfield and Koehl, 2004). Larvae exposed to water flow with the dissolved settlement cue retracted their vela, stopped swimming, and sank to the bottom of the tank. These studies on *P. sibogae* illustrate how marine natural products can mediate larval behavior, specifically targeting cellular and neurological components that directly effect settlement and metamorphosis. This mechanism of "hard-wiring" behavior into the dispersal phase of marine invertebrates is especially important for the survival of specialist opisthobranchs, many of which rely on only one or two prey species. Because few natural inducers of settlement and metamorphosis have been isolated, it is impossible to know whether these are consistently neurotransmitter-type compounds or whether specialists can also use defensive compounds (such as those reviewed here) as settlement cues.

A rarely considered aspect of chemical defenses is how predators detect and then respond to toxic compounds (Derby, 2007). Natural predators such as fish have an olfactory organ and are capable of smelling prey items (Hara, 1993; Laberge and Hara, 2001). Some amino acids have been shown to stimulate feeding in the rabbitfish *Siganus fuscescens* (Ishida and Kobayashi, 1992), and the chemosensory ability of coral reef fish was recently reviewed by Myrberg and Fuiman (2002). Research on the structure of the olfactory system, signal processing, and olfactory communication within the forebrain of fish is reviewed in Laberge and Hara (2001). The olfactory system in fish can be used to detect alarm cues from conspecifics and predators (Wisenden, 2000; Mirza and Chivers, 2002) and pheromones from conspecifics (Sorensen *et al.*, 2005).

The neurological effect of harmful algal bloom toxins on the killifish *Fundulus heteroclitus* has been investigated (Salierno *et al.*, 2006). In this work, induction of c-Fos, a protein biomarker for neuronal and regional brain activity, was evaluated when specimens were exposed to the excitatory neurotoxins domoic acid and brevetoxin B, and the paralytic neurotoxin saxitoxin. All three of these neurotoxins induced changes in c-Fos expression patterns, providing valuable foundation for future work on the neuroecology of these natural products and the biochemical and neurological mechanisms by which they control fish behavior.

Structure-activity relationships of chemical defense compounds and their detection by fish remain poorly studied. In a comparison of three diterpene natural products from the soft coral *Sinularia flexibilis* (flexibilide, sinulariolide, and dihydroflexibilide), the mosquitofish *Gambusia affinis* had a different gustatory response to each compound (Aceret *et al.*, 2001). At 1% dry weight, only dihydroflexibilide was rejected after tasting, suggesting a strong gustatory response to this compound. At 10% dry weight, all three of these diterpenes were avoided before being tasted. The structurally similar furanosesterterpene tetronic acids were also tested for their ability to deter fish feeding (Pawlik *et al.*, 2002). Even though some of these compounds from sponges deterred feeding in the Caribbean blue-head wrasse *Thalassoma bifasciatum*, the volatile compounds responsible for a distinct smell in these sponges did not inhibit wrasse feed-

ing. Research with the crude extracts of the sponge *Acanthella cavernosa* showed that fish were capable of avoiding the treated food before tasting it, suggesting an olfactory response (Ritson-Williams and Paul, 2007). Johannes (1963) noted a distinct smell from the mucus of *Phyllidia varicosa*, and Burreson *et al.* (1975) attributed this smell to the isocyano terpene 9-isocyanopupukeanane. Controlled tests of the neurological response of predators to isocyanide compounds could be applied to fish feeding assays to test whether fish can "smell" a deterrent compound before they taste it. Unfortunately, relatively few studies have tested which modality is being influenced by marine natural products. These studies provide a useful baseline for further experiments, focusing on neurological reactions of ecologically relevant fish to the well-studied natural products reviewed here.

Multimodal cues are beginning to be recognized as an important mechanism for sensory recognition (Partan and Marler, 1999). Multimodal cues are important in the mating system of freshwater sticklebacks (McLennan, 2003). Chemical cues from males are used as a distance pheromone, and visual color patterns on adult males allow for conspecific recognition. Larval fish also use a variety of modalities to detect their appropriate habitat, including olfaction, vision, and hearing (Wright *et al.*, 2005). In a test to determine which modality is most used in 18 species of reef fish, Lecchini *et al.* (2005) found that two of the species used three modalities (visual, chemical, and mechanical), six species used visual and chemical cues, and five used only one type of cue. Little is known about how adult fish use multimodal cues to detect chemical defenses. One study compared visual and chemical discrimination in the predator *Chaetodon melannotus,* and the results demonstrated that these fish use both modalities to detect *Alcyonium molle,* their soft coral prey (Alino *et al.*, 1992). A recent review discusses how fish differentiate chemical cues into olfactory and gustatory cues (Kotrschal, 2000). Stimulation of the taste system is thought to control reflexes, but the olfactory system activates conditioned (learned) behaviors. In feeding assays with color patterns and crude extracts of *Acanthella cavernosa*, a natural assemblage of reef fish ate less food with the chemical extract (Ritson-Williams and Paul, 2007). However, at reduced concentrations of extracts (1% dry weight), feeding was reduced only when extracts and color patterns were offered together. Visual and chemical defenses are likely used by many marine benthic organisms to protect themselves from fish predation. It is possible (but untested) that sponges containing isocyano terpenes have a distinct smell, but also contain other natural products that are feeding deterrents. In this way the isocyanide compounds could function as olfactory cues and work synergistically with other feeding deterrents to protect sponges and nudibranchs from predation.

Summary

By selecting examples of well-studied marine natural products, we have tried to illustrate the importance of these compounds in the ecology of the organisms that produce them. In the case of harmful bloom-forming organisms, the deterrent compounds likely play a significant role in protecting the organisms from consumers and competitors, thus allowing them to bloom under ideal environmental conditions. Many of these organisms are highly successful in areas where they are endemic, and they can become invasive when introduced to areas where their ecological attributes, in particular their chemical defenses, allow them to grow unchecked by consumers. In other organisms, the chemical defense compounds appear to play an additional role in mediating specialist predator behavior, affecting settlement and metamorphosis as well as feeding behavior.

Our understanding of the neuroecology of chemical defenses is in its infancy. Little is known about the cellular mechanisms by which defensive compounds mediate consumer-prey interactions and behavior. In cases where the neurophysiology is well understood—for example, for some marine toxins that have received clinical attention—the ecological functions of the compounds have often not been well studied.

Many marine natural products, including most reviewed here, have been shown to deter feeding by generalist consumers, but the mechanisms by which marine consumers perceive and learn to avoid natural products have rarely been investigated. We have attempted to highlight studies in marine systems that may serve as models for future studies on the neuroecology of chemical defense. The nervous systems of opisthobranch molluscs, some of which are very well described, offer an opportunity to determine how these animals detect prey items and the role that natural products play in feeding specialization. Similarly, considerable background exists on chemoreception in fish that could be linked with ecological studies on feeding behavior to better understand feeding preferences and chemical defenses of marine organisms. It is our hope that this review will stimulate future work on these and related subjects to link neuroecology and marine chemical ecology.

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