MARINE TOXINS

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Introduction

In the past decade, there has been an increasing awareness of the potential value of toxins of marine origin for the production of useful new drugs. Much of the pertinent literature on this subject has been summarized and presented in a book entitled "Marine Pharmacology" (1) published in 1969. In addition, a survey of the current status of marine biomedicinals (2) and the proceedings of the second Food-Drugs From the Sea conference (3) held at the University of Rhode Island in August 1969 under the sponsorship of the Marine Technology Society, have been published. We stand today at the beginning of a new era in marine pharmacology and, within the next decade, should know if the oceans are indeed a vast storehouse of significant new medicines.

Marine toxins, of endogenous origin, represent not only a source of potential new drugs, but are also a source of potential biotoxicological hazards due to man's increased use of the seas for recreational and food purposes. Finally, there is an increasing realization that marine toxins of exogenous origin including pollutants, such as heavy metals, pesticides, and oil residues (4), which are concentrated in biological systems, may constitute a biotoxicological problem of great importance. In the present review, only marine toxins and bioactive agents of endogenous origin will be considered.

Review of Marine Toxins and Bioactive Substances

Sea water antibiotics.—The capacity of natural sea water to destroy virus and bacterial entities has been well documented (1) although the source and nature of the antibiotic substances are still obscure. Mitchell & Wirsen (5) report that the nonmarine fungi, *Pythium debaryanum, Saprolegnia diclina, Achlya caroliniania, Isoachlya luxuriana, Thraustotheca clavata,* and *Apodchlya brachynema* are lysed by extracellular cell wall-lysing enzymes produced by specific marine micro-organisms. An *Agarbacterium sp.* was isolated from North Atlantic waters which, in pure culture, reproduced the lytic effect on *P. debaryanum* that had been observed in natural sea water. Mitchell & Jannasch (6) indicate that the marine microflora is also responsible in part for the inactivation of bacteriophage in natural sea water, perhaps mediated through the production of specific chemical antagonists.

Cyanophyta.—The marine blue-green alga *Trichodesmium erythraeum* is reported to have antibacterial properties, present in aqueous extracts, against *Staphylococcus aureus, Bacillus subtilis,* and others (*7*). In addition, Starikova (8) indicates that a lipid fraction, cyanophytine, obtained from a mixed natural growth of blue-green algae, exhibits antifungal and antiyeast activity in vitro. Among the organisms inhibited are *Trichophyton violacium, Candida albicans,* and *Saccharomyces cerevisiae.* Of major interest are the reports that toxins isolated from the fresh water blue-green alga, *Aphanizomenon flos-aquae,* may be identical to saxitoxin (9, 10), a paralytic shellfish toxin known to be produced by the marine dinoflagellate *Gonyaulax catanella.*

Pyrrophyta.—The toxins produced by marine dinoflagellates continue to be of biotoxicological importance as evidenced by the recent bloom of *Gonyaulax tamarensis* in the North Sea area which resulted in human illness and death of fishes and sea birds (11–14). The empirical formula for toxin isolated from *Gonyaulax catanella* is $C_{10}H_{17}O_4N_7 \cdot 2HCl$, and it appears to be a heat stable derivative of a purine base (15). This poison is a powerful neuromuscular blocking agent although its mechanism differs from that of curare (16). Saxitoxin inhibits sodium conductance changes associated with nerve membrane excitability both pre- and post-synaptically. In the cat tibialis anticus preparation, this toxin blocks the depolarizing action of exogenous acetylcholine. At least two toxins have been isolated from laboratory cultures of *Gymnodinium breve,* both of which appear to differ from the *G. catanella* toxin basic structure (17).

A new antifungal substance, goniodomin, has been isolated from a marine dinoflagellate, *Goniodoma sp.* A tentative molecular formula of $C_{43}H_{58}O_{11}$ has been suggested and there appear to be five hydroxyl groups, a lactone ring, four ether linkages and a dihydrogeranyl side chain in the molecule (18). Goniodomin inhibits the fungi, *Cryptococcus neoformans* and *Trichophyton mentagrophytes* and others, but shows little or no activity against bacteria.

Porifera.—Sponges continue to provide interesting bioactive materials for biomedical investigations (19–22). Sigel et al (19), investigating anticellular and antitumor activity of extracts from tropical marine invertebrates, report that alcoholic extracts of *Haliclona subtriangularis, Ircinia strobilina,* and *Chondrilla nucula* are effective cytotoxins in vitro on KB tumor cells, or in vivo against mouse lymphocytic leukemia P-388. Cytotoxic activity of extracts for KB oral carcinoma cells in culture has also been observed for the sponges *Haliclona erina, Haliclona rubens, Callyspongia plicifera, Pellina carbonaria,* and others (*20*). In addition, water and ethanolic extracts of these sponges also showed antibiotic and ichthyotoxic activity. Antibiotic compounds which consist of a group of bromination

products of 2-phenoxy-phenol and are effective against both gram negative and gram positive organisms (21) have been isolated from *Dysidea herbacea*. In this same study, antibiotic compounds obtained from *Phakellia flabellata* with the empirical formulae $C_{11}H_{11}N_5OBr_2$ and $C_{11}H_{12}N_5OBr$ were reported.

Hemagglutinins of high molecular weight have been isolated from *Cliona celata* and *Axinella sp,* and a hemolysin has been prepared from extracts of *Tethya aurantium* (22). Interestingly, although sponges have developed defensive characters such as mineralized sclerites, noxious and toxic chemical substances, and tough fibrous components, most of the sponges reported to contain ichthyotoxins and cytotoxins comprise the major natural food for a limited number of species of reef dwelling fish (23).

Cnidaria.—The occurrence of known pharmacologically active substances including histamine, tetramethylammonium, and catecholamines in the nerve net and stinging tentacles of the sea anemone *Actina equina* have been studied (24, 25) and new prostaglandin derivatives have been isolated from the gorgonian *Plexaura homomalia* (26, 27). Prostaglandins belong to a family of lipid acids, active in very low concentrations, which are believed to be regulators of many functions including smooth muscle activity, lipid metabolism, and CNS activity among others. Further studies on the structural configuration of eunicin, an oxa-bridged cembranolide diterpene obtained from the gorgonian *Eunicea mammosa,* which exhibits antibacterial activity, have also continued (28, 29).

Cnidarians that contain highly toxic tentacular nematocysts have continued to receive a great deal of attention. Studies of the poisoning by stings of the medusa *Gonionemus vertens* in the sea of Japan have revealed that in addition to typical urticarial wheals, and local edema, polyneuritis, and psychiatric aberrations also occur (30). Psychological symptoms that develop include clouding of consciousness, psychomotor excitement, delirium, and hallucinations. The toxin from *Physalia physalia* nematocysts, given in sublethal doses, has been shown to depress arterial pressure and prolong the effect of epinephrine in anesthetized rats (31). The toxin appears to have a direct, noncholinergic, nonhistaminic, stimulating action on smooth muscle. It is of interest that the nudibranch molluscs *Glaucus atlanticus* and *Glaucilla marginata,* planktonic sea slugs, store the intact nematocysts of *Physalia utriaulus* which are used in their own defense (32).

Further studies of the toxins of the highly venomous sea wasp *Chironex fleckeri,* have been made (33). The nematocysts of *C. fleckeri* have been isolated in quantity, and pharmacological evaluation of the material indicates that paralysis is due to alteration of membrane permeability (34, 35). The venom of *C. fleckeri* is antigenic in rabbits and mice, and neutralizing antibody produced in rabbits passively protects mice against the lethal, but not the necrotic, action of the venom (36). Extracts of the tentacles of this organism also possess strong hemolytic properties (37). The hemolysin has

been partially purified and considered to be a protein of molecular weight of approximately 70,000.

Toxins obtained from the anemone *Condylactis gigantea* have been found to transform action potentials in crustacean neurons into prolonged plateau potentials of up to several seconds' duration. It is suggested that the observed plateaus are caused in part by a prolonged membrane permeability after initial excitation (38–41).

Studies of the toxic components of the sea nettle *Chrysaora quinquecirrha* indicate that intoxication produces pathological changes in the heart, lungs, and kidneys of mice and that the toxic fraction may be a protein or protein complex (42).

Mollusca.—The octopus *Hapalochlaena maculosa,* a common inhabitant of the shallow waters around the Australian coast, has produced several human fatalities. Pharmacologically, the toxin extracted from the salivary glands affects both neuromuscular junctions and nerve conductivity with subsequent paralysis of voluntary muscle activity (43). There are at least two toxic moieties in the venom of *H. maculosa,* and unlike cephalotoxin, previously isolated from other species, these components are of low molecular weight and apparently nonantigenic. Further studies on the pharmacological actions of eledoisin, a peptide hypotensive agent, which is another constituent of cephalopod venom, have been made (44–48).

Aplysin, a term originally used to designate a toxic material obtained from the digestive gland of the sea hare *Aplysia californica,* has also been used to designate a specific organic bromine compound obtained from *Aplysia kurodai,* although the relationship between these materials is obscure. Winkler (49) indicates however, that the digestive gland of *A. californica,* a source of the toxin, is also the richest source of organic bromine compounds in this organism.

Studies of the red cell agglutinins of many mollusc species including *Anodonta cygnea, Tridacna niloticus, Haliotis asinina,* and others (50–53) indicate the presence of hemagglutinins for a number of vertebrate erythrocytes. These hemagglutins display a specificity analogous with the naturally occurring iso-hemagglutinins present in vertebrate serum and may be immunoglobins.

One of the most interesting areas of research continues to be the study of antiviral activity of substances isolated from mollusc tissues. Li et al (54) report reduced tumor incidence in hamsters inoculated with Adenovirus 12 and treated with clam extracts. Inhibition of viral oncogenesis was observed in hamsters after treatment with a series of subcutaneous injections of extracts made from tissue of the clam *Mercenaria mercenaria.* Incidence of subsequent formation of solid subcutaneous tumors was reduced by more than half in these treated animals.

Arthropoda.—A screening program to determine the extent of toxic crab

species in the Pacific was undertaken by Hashimoto et al (55). The screening included 1000 specimens belonging to 72 species in 8 families. Of these, only 3 species, *Zosimus aeneus, Platypodia granulosa,* and *Atergatis floridus* contained toxic specimens. The toxicity of these three species of xanthid crabs was determined by a mouse bioassay method, and large individual variations in crab toxicity were common. Interestingly, in most cases, the exoskeleton contained the largest amount of toxin (56, 57). Using a partially purified crab toxin that exhibited some of the pharmacological properties reported for saxitoxin, chromatographic analysis using saxitoxin were indistinguishable. Thus, it has been suggested that crab toxin may be identical or closely related to the dinoflagellate toxin (58).

Echinodermata.—Three new holothurinogenins, the aglycone portion of sea cucumber saponins from *Bohadschia koellikeri,* have been identified as ternaygenin ($C_{31}H_{48}O_4$), koellikergenin ($C_{30}H_{46}O_4$), and seychellogenin ($C_{30}H_{46}O_3$) by Roller et al (59). The unsaponifiable fractions obtained from *Stichopus japonicus* and *Holothuria tubulosa* contain mixtures of delta-5 and delta-7 (C_{27}, C_{28}, and C_{29}) sterols with the delta-7 series predominating (60).

The biosynthesis of sterols, squalene, and triterpenic alcohols from C-14 labelled acetate has been investigated in *Stichopus japonicus,* and it was observed that only squalene was labelled in this experiment. It is suggested that holothurins have an exogenous origin, or are transformation products from food constituents (61).

The purified saponins obtained from the starfish *Asterias amurensis,* asterosaponin A and asterosaponin B, have been found to have different relative potencies when tested on the rat phrenic nerve-diaphragm preparation. Asterosaponin A is relatively more potent than asterosaponin B in blockade of indirectly elicited contraction. These observations have been interpreted in terms of surface polarity differences among the sugars comprising glycosidic chains in the two toxin structures (62).

Chordata.—Tetrodotoxin, a naturally occurring highly toxic heterocyclic compound present in puffer fish, containing a guanidinium group and a unique orthoester moiety, blocks nerve conduction by interference with sodium conductance. In an attempt to identify the functional groups of the tetrodotoxin molecule, Ranney et al (63) studied the pharmacological activity of several synthetic guanidine esters. Some of these compounds were neuroactive, but the mechanism of action appeared to differ from that of tetrodotoxin and none of the esters approached tetrodotoxin in toxicity.

On the chemical level, tetrodotoxin appears to have a specific interaction with cholesterol and other lipids in the axon-excitable membrane (64, 65) and it promotes the release of thiamine from the membrane of perfused rat and frog nerve preparations (66). In addition, in the presence of tetrodotoxin, the slow polymerization of soluble microsomal structural proteins of

low particle weight obtained from sheep brain is accelerated. The toxin appears to have no depolymerizing effect on similar preparations of high particle weight (67). Extensive studies of the pharmacological and neurophysiological properties of tetrodotoxin on invertebrate and vertebrate organisms continue to be reported (68–73).

Tetrodotoxin is a constituent of the eggs of the puffer as well as other tissues. Eggs from about 10 genera of fishes are also known to be toxic, but the toxic moiety appears not to be tetrodotoxin in most cases. The eggs of the marbled sculpin *Scorpaenichthys marmoratus* contain a toxin that inhibits growth of cells in tissue culture and produces necrosis in the liver and spleen. The toxin appears to be a protein or a protein complex in the eggs (74).

The integument of the sea bass *Pogonoperca punctata* has been observed to contain a toxic substance of low molecular weight which causes ciguatera-like effects in cats (75). On thin layer chromatography 4–5 toxic components have been separated which give a positive Dragendorff reaction but are negative to both biuret and ninhydrin reagents. A toxic fraction obtained from the secretions of a related fish species *Grammistes sexlineatus* appears to be identical, and a wide distribution of a similar toxin in members of the subfamily Grammistinae is suggested.

The distribution, chemistry, and pharmacology of ciguatera toxins, which are responsible for intermittent ichthyosarcotoxism throughout the world, continue to be investigated (76–81). Although ciguatoxin, prepared from the liver and flesh of the moray eel *Gymnothorax javanicus,* is an in vitro anticholinesterase, it has not been found to be an in vivo anticholinesterase. Respiratory failure and death due to ciguatoxin are not functions of cholinesterase inhibition as previously speculated, although the toxin may have widespread action at cholinergic junctions (82).

Conclusions

The biomedically interesting toxins of endogenous marine origin have continued to receive much attention both from the aspects of toxicological importance and pharmacological potential. The focus of attention regarding marine toxins appears to be concentrating on the microflora of the sea, especially the phytoplankton organisms. The most important problems in marine toxicology, ciguatera poisoning, paralytic shellfish poisoning, and massive fish and bird kills have already been traced to the dinoflagellate populations of the oceans. In the present review, it has been noted that the saponin toxins of sea cucumbers may have their origin in the food chain. Finally, marine blue-green algae have been reported to produce a toxin similar to dinoflagellate toxin, and it is possible that either the blue-green algal toxin or saxitoxin produced by dinoflagellates may be the source of the similar material obtained from toxic crabs.

It would appear therefore, from the marine toxicological aspect, that

very close attention should be given to the presence of pollutants and other environmental variables that may affect the growth of potentially hazardous marine microflora, especially in areas experiencing new or increased red tide and fish kill activity.

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