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BIOMEDICAL POTENTIAL OF THE SEA

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Abstract - Marine life forms studied in recent years have yielded a variety of organic compounds possessing known or novel pharmacologic and toxicologic activities in mammalian species. Evidence available to date suggests that the sea offers a rich reserve of novel organic molecules which, as such or in structurally modified form, may be useful to mankind either as new drugs to combat disease or as biochemical, physiologic and pharmacologic tools in biomedical research.

INTRODUCTION

This overview of developments in marine pharmacology during the last decade deals primarily with organic compounds isolated from various marine organisms in different laboratories and pharmacologically characterized to variable extents. Although the contributions of other investigators are cited, the bulk of the data presented were generated in the author's laboratories.

Biomedical potential of the sea has been known probably for thousands of years, but a revived interest in it is a result of recent application of new chemical and biological tools which has led to the isolation of biologically active compounds from marine organisms. Earlier reviews relative to biologic activities in crude extracts of the organisms or somewhat purified fractions thereof include those by der Marderosian (1), Giloli and Giacobazzi (2), Hartwell and Wood (3), Russel (4), Ruggieri (5) and Faulkner (6). More recent reviews (Ref. 7-9) have largely dealt with pharmacologic activities of pure compounds of marine origin.

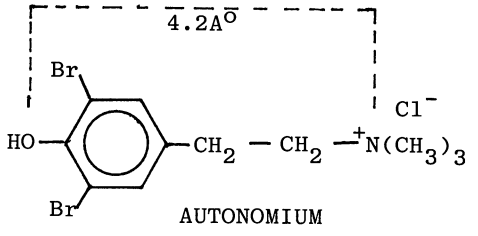
CARDIOVASCULAR-ACTIVE COMPOUNDS

Perhaps the largest number of extracts of marine invertebrates and their purified fractions show significant cardiovascular activities on the mammalian systems (Ref. 10a). This is primarily due to the presence of either histamine derivatives which was demonstrated in various sponges (Ref. 10b) or calcium as is aften the case with gorgonians. However, some very unusual and potent compounds have nonetheless emerged.

Dual adrenergic and cholinergic compound

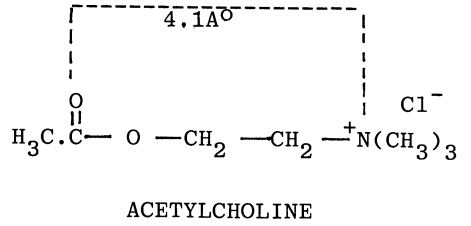
Pharmacology of organic compounds of synthetic or natural origin, possessing activity on the autonomic nervous system as it regulates cardiovascular physiology, is usually understood in terms of these substances mimicking the actions of nor-adrenaline and acetylcholine, the two neurotransmitters present in the autonomic nerve terminals. An unusual compound, autonomium *(1)*, isolated from *Verongia fistularis* (Ref. 11) exhibited not only α - and β - adrenergic activities blockable by the respective antagonists, but it also possesses cholinergic activity typical of acetylcholine *(2)*. The distance between the quaternary nitrogen and the oxygen-bearing carbon in autonomium is 4.2 A° as compared with 4.1 A° for the same distance in acetylcholine (Ref. 9). This may perhaps explain the cholinergic activity in autonomium. Likewise, the adrenergic activity may be gauged from the phenethylamine structure typical of adrenaline *(3)*. It is not uncommon to find biologic activities in compounds with structure and interatomic distances similar to those of known bioactive compounds.

Autonomium also shows central nervous system (CNS) stimulant effect in mice as gauged by a significant increase in spontaneous motor activity (Ref. 11). The importance of such dual autonomically active compounds in marine environment is unknown, but it poses a question on the possibility for occurence of similar compounds in mammalians. Such compounds within CNS could conceivably play a role in regulating behavior, since much has been written on the balance between the cholinergic and the adrenergic systems within CNS required for normal behavior of both animals and man.



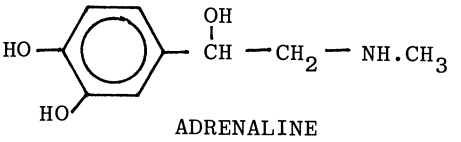
AUTONOMIUM

(1)



ACETYLCHOLINE

(2)



ADRENALINE

(3)

Cardiotonic peptides

Of the three neuro- and cardio-toxic polypeptides from *Anemonia sulcata* described by Beress *et al* (12), ATX-II contains 47 amino acid residues and is probably the most potent of the group on crustacian as well as mammalian hearts (Ref. 13). Although considered largely as toxic and labeled so by the discoverers, these sea anemone toxins are potent cardiotonic substances and comparable in many ways to anthopleurin-A (APA) from sea anemone *Anthopleura xanthogrammica* described by Shibata *et al* and Norton (15). ATX-II has been recently made available commercially for use as a physiological tool to characterize sodium channels in nerve and muscle membranes.

The cardiotonic peptide, AP-A, is the more extensively studied of the three closely related peptides isolated from two species of *Anthopleura* (Ref. 15). It contains 49 amino acid residues with three intramolecular disulfide bridges at cys-cys residues 4-46, 6-36, 29-47. It is present in *A. xanthogrammica* in amounts relatively larger than other anthopleurins. The increase in the force of myocardiac contractility, which AP-A produces, appears to be the result of a direct effect on the heart muscle, since this action is not affected either by reserpine pretreatment which depletes the muscle of neurotransmitters stored in the heart tissue or by adrenergic blocking agents which prevent norepinephrine from acting, were it released by AP-A. The Na^+, K^+-ATPase also seems unaffected by AP-A. What is interesting is also the reported finding that the cardiotonic action of AP-A is affected by Ca^{++} to a far less extent than most other known heart stimulants (Ref. 15). It has been claimed that translocation of intracellular Ca^{++}, rather than influx of extracellular Ca^{++}, may be involved in the mechanism of action of AP-A (Ref. 16).

Attempts to prepare smaller fragments of AP-A by enzymatic or other degradative means, retaining cardiotonic activity have failed so far (Ref. 15). However, other molecular modifications have yielded data which would suggest that the cardiac activity may reside more likely in a relatively smaller fragment of the whole peptide. This is not uncommon in biological systems, as has been borne out by recent examples of endorphins and enkephalins. Perhaps a clearer case is the peptide gastrin, which regulates gastric juice production but which in action is replaceable by a synthetic pentapeptide called pentagastrin. The latter is nearly one-fifth the size of the naturally ocurring peptide.

Supporting this thought is the marine derived tetrapeptide, FMRFamide, Phe-Met-Arg-Phe-NH_2, which is a molluscan neuropeptide implicated in cardioregulation in bivalve molluscs (Ref. 17). Although this compound has many actions on nerve amd muscle tissues, it appears to invariably increase cAMP production in the cardiac tissue. Both mammalian and molluscan hearts are stimulated by FMRFamide. Thus it remains to be seen if AP-A activity can be reproduced by a smaller peptide which would also be orally absorbable and

active, a property not enjoyed by AP-A. An important contribution of marine peptides is that, for the first time in the history of cardiac drugs, structures other than the digitalis aglycones and those neurotransmitter-related have been found to possess cardiotonic activity, especially molecules of the peptide type.

Vasoactive Compounds

Urotensin-I. Teleosts and elasmobranch fishes contain a neurosecretory system known as urophysis, in addition to the hypothalamic-neurohypophyseal system well known in mammals. Of a number of putative hormones of the fish isolated from the urophysis, Urotensin-I, a straight chain 38-residue peptide, produces a sustained lowering of blood pressure in all mammalian species tested so far (Ref. 18 & 19). In both rat and dog, 10^{-15} moles of Urotensin-I injected intravenously lowers blood pressure for several hours. The sheep and primates also react the same way. The hypotensive effect has been claimed to be the result of selective vasodilation of mesenteric vascular bed (Ref. 19). Whether or not this large peptide also can yield a relatively small molecule with parent activity remains to be seen.

Palytoxin. One of the more interesting vasoactive molecules is palytoxin (PTX) isolated from various *Palythoa* spp. inhabiting Caribbean (Ref. 20 & 21) and Pacific (Ref. 22 & 23) oceans. Structure of PTX has recently been elucidated by Moore and Bartolini (24). This polyhydroxy, long chain, macromolecule is the most potent marine toxin (Ref. 25) and also the most potent coronary vasoconstrictor substance (Ref. 9) known to date. As little as 1.6 x 10^{-17} moles can produce near total constriction of the coronary artery in an isolated guinea pig heart (Ref. 26). Although this potent coronary vasoconstriction has been tentatively ascribed as the mechanism of PTX toxicity (Ref. 9), the toxin also has direct effect on a number of other muscle and nerve tissues (Ref. 25 - 29). The action of PTX on nerve membranes, as observed by intracellular and extracellular microelectrode recordings of neuronal activity in the coupled Retzius cells of Horse Leech ganglia (Ref. 26), indicates that mechanism of PTX on the nerve tissues is clearly different from that of tetrodotoxin (TTX) which is a well known sodium channel blocker. In both the nerve and the conducting system of the heart muscle, PTX appears to simulate the effects of large doses of extracellular K^+ (Ref. 26, 29 & 30). The membrane resistance as well as resting potential of single Retzius cell are unaffected by PTX (Ref. 26). In contrast to these observations, Wiedmann (31) observed a decrease in the membrane resting potential in rabbit papillary muscle. However, it is difficult to determine if the latter observation was really a result of the effect of PTX, since a partially purified fraction of *Palythoa*, and not pure PTX, was used in Wiedmann's experiments.

Perhaps the most interesting aspect of PTX is its effect on the electrocardiogram (EKG) of mammals such as the rat, the dog, and the guinea pig (Fig. 1). It elevates the T-wave and the S-T segment (Ref. 26 & 29), similar to what is observed in the clinical diagnostic EKG of patients suffering from variant or Prinzmetal angina. Intravenous infusion of 0.1M KCl also produces somewhat similar changes. It is conceivable that PTX induces a coronary vascular spasm analogous to the spasm experienced by the variant angina patients. This PTX may serve as a physiological *cum* pharmacologic tool to study animal models of this disease.

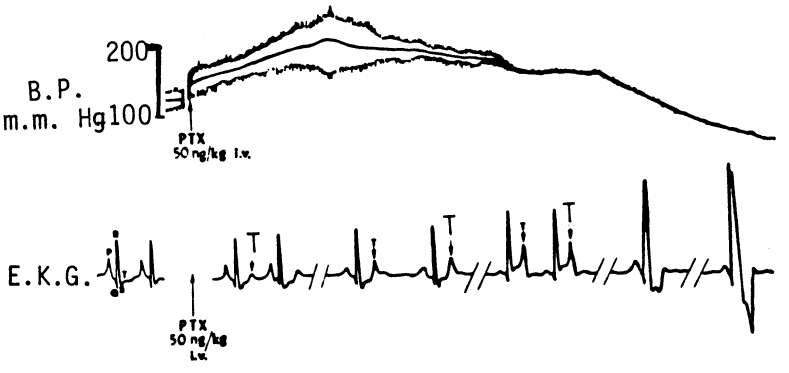
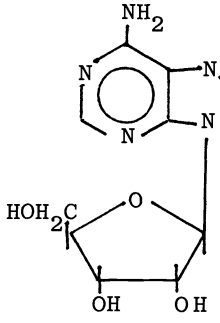
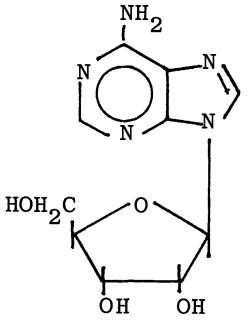


Fig. 1. Effect of palytoxin (PTX) on the blood pressure and EKG of an anesthetized dog.

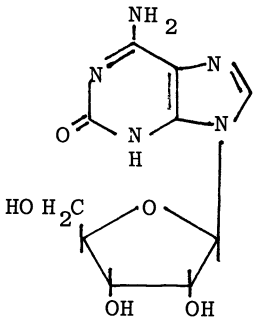
Marine nucleosides. Our interest in marine nucleosides began when we observed that a substance isolated from a sponge, *Dasychalina cyathina* produced an asystole in an isolated spontaneously beating guinea pig heart (Ref. 32). This compound was subsequently shown to be adenosine *(4)* (Ref. 33 & 34). Another nucleoside, spongosine *(5)*, was isolated from an extract of a sponge, *Cryptotethia crypta*, while being followed for the isolation of another asystolic activity. It must be pointed out that cytosine arabinoside *(8)*, an effective anticancer drug being used for a decade or more in treating leukemia, was developed as a result of semisynthetic manipulation of an unusual nucleoside present in this sponge.



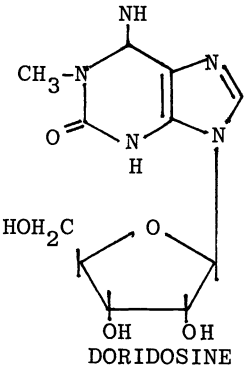
ADENOSINE *(4)*



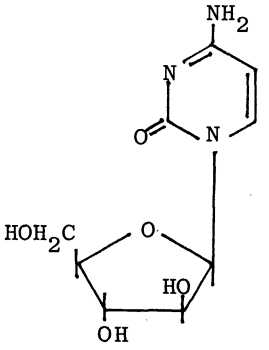
SPONGOSINE *(5)*



ISOGUANOSINE *(6)*



DORIDOSINE *(7)*



CYTARABINE *(8)*

A comparative cardiovascular study of various marine nucleosides in our laboratories have shown that these compounds reduce both rate and force of contraction of the heart, the relative potencies being adenosine > doridosine *(7)* ≥ isoguanosine *(6)* > spongosine (Fig. 2 & 3). However, their potencies in increasing the coronary flow as a result of dilation of the coronary arteries are adenosine > spongosine > isoguanosine > doridosine (Fig. 4). Caffeine, a blocker of adenosinergic receptors, blocks the effect of marine nucleosides on the force and rate of myocardiac contractility (Fig. 5). It also blocks their effect on the coronary flow, but somewhat less effectively (Fig. 6). Whether or not different types of purinergic receptors are involved in mediating the cardiac muscular and vascular effects remains an open question.

ANTIBIOTICS

Being experimentally the easiest of most bioassays, the antibiotic activity of marine derived extracts, fractions and pure compounds has been reported with the largest frequency and numbers (Ref. 1, 5, 35 - 37). Despite such reports appearing for the last three decades, no antibiotic of clinical significance has emerged. This is perhaps understandable in view of the fact that several broad spectrum as well as specifically potent antibiotics have been available for quite some time and it is very difficult to surpass their effectiveness.

Recently, however, Schmitz *et al* (38 & 39) have reported on a novel polyether antibiotic, acanthifolicin, isolated from the sponge *Pandaros acanthifolium*. In addition to being an interesting molecule structurally, it also exhibits

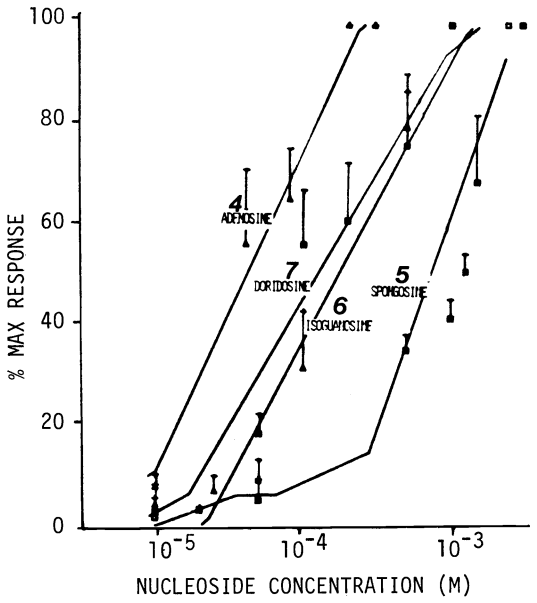


Fig. 2. Inhibitory effect of marine nucleosides on the rate of contraction of the isolated guinea pig heart.

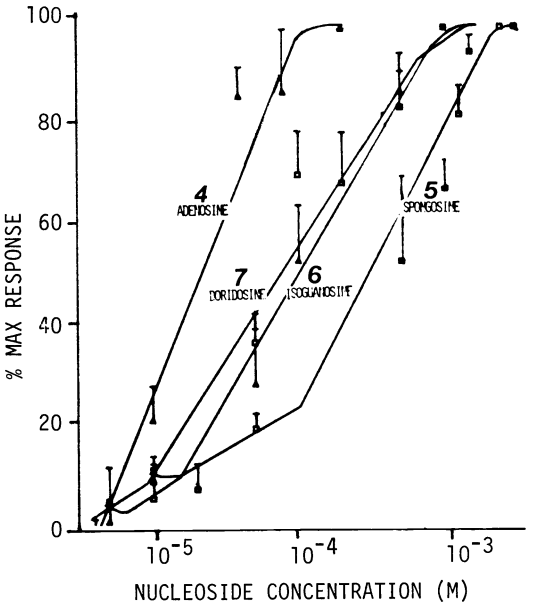


Fig. 3. Inhibitory effect of marine nucleosides on the force of contraction.

Figures 2-5
4 ADENOSINE; *5* SPONGOSINE;
6 ISOGUANOSINE; *7* DORIDOSINE

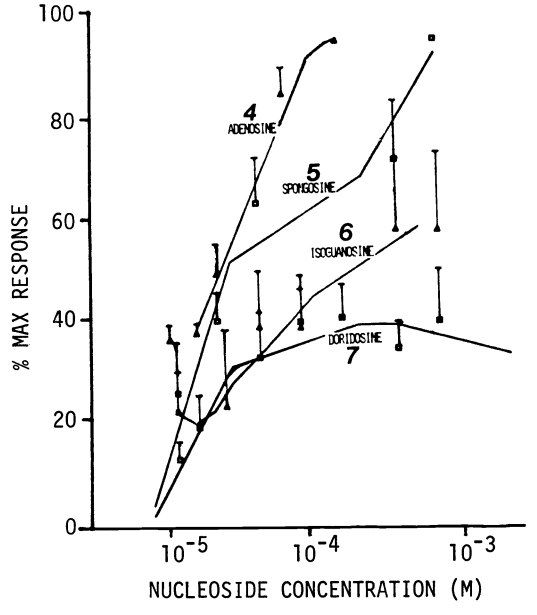


Fig. 4. Increase in the coronary flow as a result of the effect of marine nucleosides.

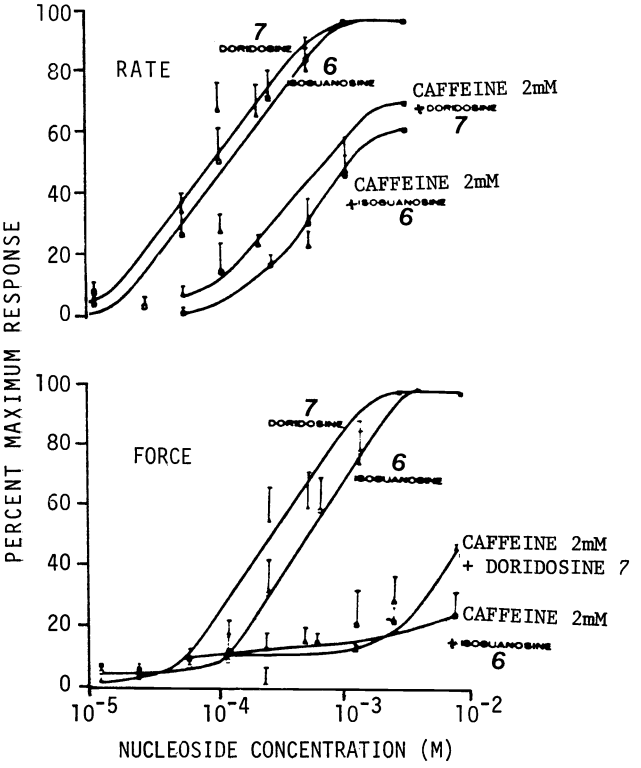


Fig. 5. Blocking effect of caffeine on the rate(upper) and force(lower) of myocardiac contraction caused by the nucleosides.

cytotoxic activity against certain cell lines. Another polyether cytotoxic compound, okadaic acid, has been isolated from two sponges of genus *Halichondria* (Ref. 40). These types of polyether compounds have recently drawn much attention, but their toxicity appears to be relatively high. Whether or not we will have biomedically or clinically useful compounds out of such candidates remains to be seen. There is no question, however, that these ethers add to the other highly bioactive compounds in marine invertebrates to be realized and exploited.

ANTIVIRAL AND ANTICANCER AGENTS

Just about every marine natural product research group, be it in the exotic marine environment such as that of Hawaii and Tenerife or in the boondocks of Oklahoma, has enthusiastically reported on the "anticancer" activity of marine derived extracts, fractions and compounds. This has been largely because of the availability of screening facilities of the U.S. National Cancer Institute. In this screening program, 2 or 3 cell lines are exposed to limited concentrations of the test substance to determine cytotoxicity. Active compounds are also tested in tumor bearing or leukemic mice to determine their survival as compared to the controls receiving only the vehicle. Like the antibiotic area, thousands of extracts, fractions and pure compounds have been reported as active (Ref. 41 - 43), but in most cases this may be considered only as an index of their nonspecific cytotoxicity rather than anticancer activity or even potential.

Recently, however, much attention has been paid to one group of novel compounds, didemnins, reported by Rinehart *et al* (44 & 45) as antiviral and cytotoxic peptides. These cyclic depsipeptides have been isolated from the Caribbean tunicates, *Tridemnun* species. Interesting chemical features of these molecules are that they contain not only statine in a new stereochemical form but also a new structural unit, hydroxyisovalerylpropionic acid (HIP). Among the didemnins A, B and C reported, didemnin B appears to be the most potent in blocking the growth of L-1210 mouse leukemic cells as well as inhibiting the *Herpes simplex* virus.

In view of the recent uproar in Washington, D.C., relative to clinical testing of investigational new anticancer drugs, which to date have enjoyed an easier path for first entry into human as compared to other investigational new drugs, it is difficult to predict the clinical utility of didemnins. Many hurdles of safety and efficacy have to be crossed by a new drug before it finds a place in therapeutics. However, the biomedical potential of such and related compounds yet to be discovered is apparent.

ENZYME INHIBITORS

While pursuing the bioassay guided isolation of a CNS-depressant activity in the crude extracts of sea hare, *Aplysia dactylomela*, it was apparent from the purified fractions that we were working with something which potentiated the action of pentobarbital in mice and rats. Consequently, an unsaturated and halogenated cyclic ether, dactylyne *(9)* was isolated (Ref. 46). This compound produced a dose dependent prolongation of pentobarbital-induced hypnosis in animals but by itself did not have any other apparent effects (Ref. 47). Detailed studies on the mechanism of action of *(9)* revealed that it inhibits the metabolism of pentobarbital and thus prolongs the barbiturate hypnosis (Ref. 48). Other related halogenated cyclic ethers with exocyclic enine features also showed this pentobarbital metabolism inhibiting property, but among several compounds tested *(9 - 13)*, *(9)* was the most potent followed by compound *(11)* (Ref. 49). Table 1 shows blood levels of pentobarbital in rats treated with various inhibitors of drug metabolism, along with the duration of hypnosis and half-life of disappearance of pentobarbital in corresponding groups of treated animals (Ref. 52).

Since pentobarbital is metabolized by oxidation with the help of hepatic Cyt-P_{450}, we had proposed that through inhibition of this enzyme dactylyne might prove to be a general drug metabolism inhibitor of clinical value (Ref. 50). Subsequent work done elsewhere has revealed that *(9)* does indeed bind with Cyt-P_{450} as determined by spectral changes of the enzyme and that it consequently inhibits the activity of the enzyme (Ref. 51). Enzyme inhibitors, especially in molecular biology are becoming increasingly important in controlling cellular processes. The marine derived enzyme inhibitors should

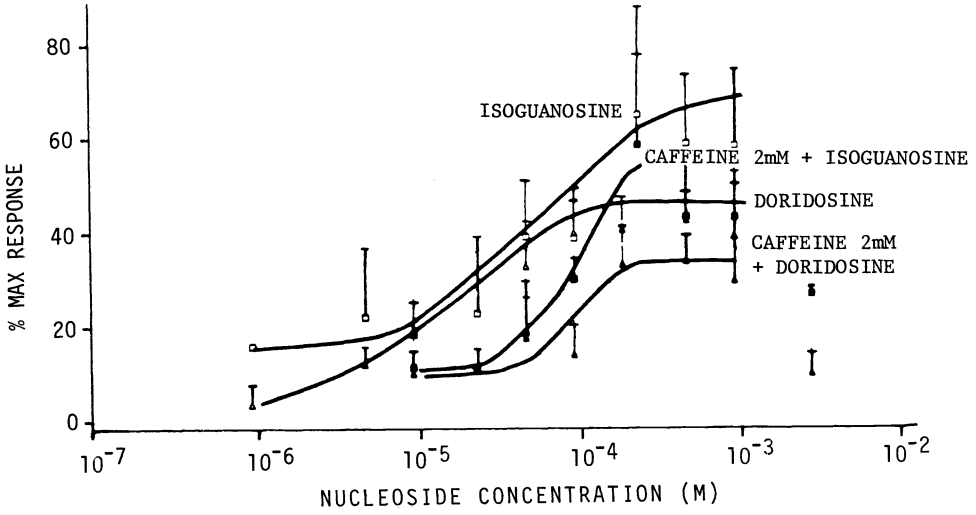
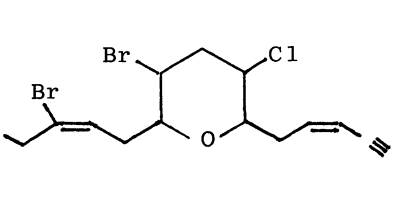
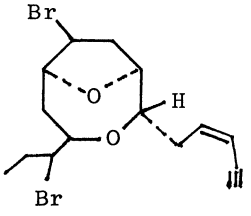


Fig. 6. Blocking effect of caffeine on the coronary flow as affected by isoguanosine and doridosine. Similar effect is seen also with other nucleosides.



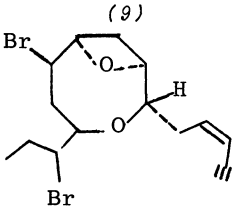
DACTYLYNE

(9)



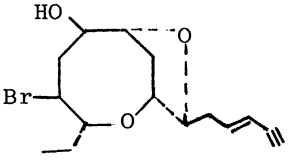
ISOLAUREATIN

(10)



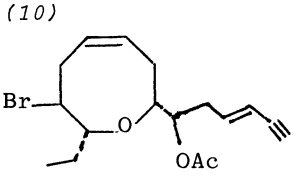
LAUREATIN

(11)



LAUREFUCIN

(12)



LAURENCIN

(13)

TABLE 1. Blood concentration and half-life of pentobarbital[a] (PB) in rats pretreated with various metabolism inhibitors

Treatment[b] (n)	Sleep-time (min.)	PB conc. (mcg/ml) at 60 min.	PB conc. (mcg/ml) on awakening	Half-life[c] (min.)
control(10) [saline]	65 ± 3.0	11.1 ± 1.3	10.8 ± 0.7	112 ± 15
Isolaureatin(20)	97 ± 6.0*	18.0 ± 1.5*	12.4 ± 0.6	147 ± 23
Dactylyne(10)	120 ± 7.5*	17.0 ± 1.0*	13.1 ± 0.9	183 ± 22
SKF-525A[d](10)	108 ± 4.8*	15.1 ± 1.2*	11.4 ± 0.7	135 ± 22

[a] 25mg/kg dose given intravenously.
[b] 10mg/kg dose of each inhibitor given intraperitoneally 30 min. prior to PB.
[c] The disappearance followed a two compartment model. The values are mean ± S.E. of the β-phase disappearance.
[d] This is a well known drug metabolism inhibitor included for comparison.
* Significant at $P < 0.05$ or less levels.

be extensively screened for activity against other enzymes. Also, rigorous structural modifications for structure-activity correlational studies may yield specific compounds with potent desired activities.

HYPOTHERMIC COMPOUNDS

Marine nucleosides *(5)* and *(7)* were found to produce significant hypothermia in mice and guinea pigs when given in doses above 10-20 mcg/kg systemically as well as directly into the lateral ventricles of the brain. In lower doses, a transient hypothermia was followed by hyperthermia typical of all doses of adenosine. Table 2 shows the comparative body temperature lowering effects of various nucleosides studied in conscious guinea pigs.

The cardiovascular effects of marine nucleosides clearly bring about both slowing down of the heart and hypotension, but both these effects are short lasting, at least in the case of spongosine *(5)*. The hypothermia occurs much later and peaks more than 30 minutes after the blood pressure effects are over. Thus the temperature lowering appears to be unrelated to circulatory effects of these nucleosides. More likely, the effect is a result of central action within the cerebral and hypothalamic thermoregulatory centers. It is too early to predict the practical value of this hypothermic action of marine nucleosides, but the observation is of interest in that it provides the first lead for possible involvement of purinergic receptors in thermoregulation.

TABLE 2. Hypothermic effects of marine nucleosides in conscious guinea pigs

Treatment[a]	Dose (mcg/kg)	Body Temperature Response[b]		
		Peak temp. (°C)	Peak time (min.)	Duration (min.)
Adenosine*(4)*	100	+0.8 ± 0.2	156	130
Isoguanosine*(6)*	50	-0.6 ± 0.2	36	80
Spongosine*(5)*	50	-1.3 ± 0.3	50	96
+ Theophylline[c]		-0.7 ± 0.2	15	72
Doridosine*(7)*	20	-1.8 ± 0.2	60	240
+ Theophylline[c]		-1.3 ± 0.2	60	204

[a]Nucleosides were injected into the lateral brain ventricle as solutions at 50 mcl/kg.
[b]Values of temperature are mean ± S.E. of 5-12 animals.
[c]Theophylline was given in 10-15 mg/kg doses, i.p., 30 min. prior to nucleoside injection.

Other hypothermic compounds of marine origin include saponins from *Holuthuria floridana* which are potent hypothermic agents. These types of compounds, however, are generally cardiotoxic and also produce hemolysis. Although animals given one of the marine saponins and sapogenins exhibited a marked depression of motor activity, the most prominent effect was on body temperature. Whether or not hemolysis can lead to release of endogenous substances which cause hypothermia remains an open question. Ouabain, a well known cardiotonic glycoside is also a saponin. In relatively high doses (5mg/kg), it too lowered body temperature of mice though only moderately (0.6°C), being accompanied by convulsions but no hemolysis. In contrast, 5mg/kg of the marine saponin lowered body temperature by 1.4°C, exhibited no convulsions in animals but did produce mild hemolysis.

Unlike marine nucleosides the marine saponins are relatively toxic. What changes, if any, in toxicity can be affected by molecular modification of the parent compound remains to be determined. Safe and effective hypothermic agents can always find their place in therpeutics of febrile state.

Lastly, a few years ago, considerable work was being done on the immunosuppressive activity of an alcoholic extract of the sea squirt, *Ecteinascidia turbinata*. The extract as well as several purified fractions were found by Lichter *et al* (53) to inhibit DNA synthesis in lymphocytes after mutagenic stimulation by lectins. Subsequent studies have indicated that the suppressor activity is exerted by cells possessing T lymphocyte characteristics (Ref. 54). It is possible to use the extract or even semi-purified fractions to

further study suppression and regulation of immune response in mammalian *in vitro* and *in vivo* systems, but much work done with crude extracts will always remain to be confirmed with isolated pure compounds. Unfortunately, despite attempts over several years it has not been possible to isolate this important activity in a pure form.

CONCLUSION

Life perhaps began in the sea. The sea has also yielded valuable insights into many life processes as we understand these in mammals. Undoubtedly, the future food, mineral and energy resources are also going to come from the sea. This review reflects yet another aspect of the riches of the sea, namely the biomedical potential. In time to come we will witness at least two avenues of biomedical significance emerging from the sea. Clearly, the evidence of novel and pharmacologically active compounds marks the beginning of exploration of the sea for future therapeutic agents. We should also experience an increasing use of marine life forms as pharmacologic and toxicologic models for screening as well as for indepth mechanistic studies.

For the cynic questioning the biomedical value of the sea, it is important to point out that only handful of laboratories and perhaps a score or two chemists and pharmacologists have been investigating the marine resource. This compares extremely meagerly with hundreds and perhaps thousands of similar investigators who have in the course of at least a century investigated terrestrial resources for drugs. What is required is that more investigators, especially from the drug industry, take a dip in the oceans to seek the pearls awaiting discovery.

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