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Palytoxin: Membrane mechanisms of action☆

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ABSTRACT

Palytoxin is a marine toxin originally isolated from the zoantharians of the genus *Palythoa*, but now is found in marine organisms ranging from dinoflagellates to fishes. With a MW of 2680, it is one of the largest nonpolymeric natural products ever found. Its complex structure has been elucidated and total synthesis has been achieved. With an LD_{50} of 25 ng/kg for rabbits (the most sensitive species), it is one of the most lethal marine toxins. It binds to the Na,K-ATPase specifically with a K_D of 20 pM. It has a unique action on the Na,K-ATPase, converting the pump into an ion channel and resulting in K^+ efflux, Na^+ influx and membrane depolarization. As a result palytoxin causes a wide spectrum of secondary pharmacological actions. By acting like a key to unlock the internal structure of the Na,K-ATPase, palytoxin holds promise as a useful tool for investigation of the pump molecule.

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Palytoxin is a marine toxin originally isolated from zoantharians of the genus *Palythoa*. A colony of *Palythoa caribeaorum* is shown in Fig. 1. The toxin was discovered by three independent groups several decades ago: from *P. caribeaorum* and *P. mammilosa* in Jamaica and the Bahamas by Attaway (1968) and Attaway and Ciereszko (1974), from *P. tuberculosa* in Okinawa by Hashimoto and his associates (Hashimoto et al., 1969; Kimura et al., 1972; Hashimoto, 1979), and from *P. toxica* in Hawaii by Moore and Scheuer (1971). The occurrence of the toxin has now been found to be more widespread than originally thought. Besides *Palythoa*, it is produced by species of another zoantharian genus *Zoanthus*. Palytoxin and various analogues have also been detected in a variety of marine organisms including a sea anemone, polychaete worm, dinoflagellates, alga, crab and fish (Table 1). The presence of palytoxin in fishes implicates it in ciguatera seafood poisoning and thus it poses a potential danger to public health. In fact, it was during the initial search for agent(s) causing ciguatera that palytoxin was discovered serendipitously (Hashimoto et al., 1969; Moore and Scheuer, 1971), and the causative agent for ciguatera has now been attributed mainly to other toxins, ciguatoxin and maitotoxin, even though palytoxin still plays a role in ciguatera (Yasumoto and Satake, 1996). Recently, palytoxin and an analogue, ovatoxin-a, have been implicated as the causative agents in toxic outbreaks due to algal blooms of the dinoflagellate *Ostreopsis ovata* along the Ligurian coasts of Italy in 2005 and 2006 (Ciminiello et al., 2006, 2008). Because of its importance to public health, a method for isolating palytoxin for studies has been published (Béress et al., 1983).

The chemical structure of palytoxin has been elucidated (Moore and Bartolini, 1981; Uemura et al., 1981; for review see Moore, 1985). It turns out that the palytoxin molecule is one of the largest and most complex natural products known to date (Fig. 2). Its molecular weight of 2680 far surpassed that of any other natural substances (except for biopolymers) discovered until then, and the complexity (elemental composition, $C_{129}H_{223}N_3O_{54}$) of its chemical structure is unprecedented. Even more remarkable is that

Abbreviation: Na,K-ATPase, Na^+, K^+-adenosine triphosphatase.

☆ Dedicated to the memory of Professor Ernst R. Habermann (1926–2001), recipient of Redi Award 1991, International Society on Toxinology.

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Fig. 1. The Caribbean zoantharian *Palythoa caribeaorum* (center) (Photo by C.H. Wu).

in spite of the presence of 64 chiral centers, with theoretically possible stereo-isomers numbering in the astronomical range, its absolute stereochemistry has been elucidated (Cha et al., 1982; Moore et al., 1982b). Because of its very large size and absence of repeating units, determination of the entire structure including stereochemistry was truly a "tour de force", as was the subsequent synthesis by Kishi and his associates (Armstrong et al., 1989a,b), a feat that has been likened to scaling the Mount Everest of organic chemistry (Crawford, 1989; Mann, 1989).

The estimated LD_{50} after intraperitoneal injection of palytoxin, is 25 ng/kg for rabbits (the most sensitive species) and 50 ng/kg for mice (Kaul and Daftari, 1986), the latter is about 200 times more lethal than tetrodotoxin, and thus ranks among the most potent of all marine toxins. The extreme lethality has long been known to native Hawaiians, for they made a spear poison from an extract of *limu-make-o-Hana* 'the deadly seaweed of Hana' which was subsequently identified as *Palythoa toxica* (Moore and Scheuer, 1971; Moore et al., 1982a). Since palytoxin is toxic at extremely low concentrations, several methods have been developed to meet the needs for a sensitive, specific and rapid assay for its detection and quantification in contaminated sea foods (Levine et al., 1988; Bignami, 1993; Corpuz et al., 1994).

Palytoxin attacks all animal cells that have been studied and causes a very wide spectrum of pharmacological effects (Wiles et al., 1974). For a survey of the various pharmacological actions of palytoxin, several reviews may be consulted (Ibrahim and Shier, 1987; Habermann, 1989; Frelin and Van Renterghem, 1995; Sauviat, 1992; Ito and Urakawa, 1982; Wu and Narahashi, 1988). Because the literature on palytoxin is so extensive, this review will focus only on the membrane mechanisms of action of the toxin. Palytoxin causes skeletal, smooth and cardiac muscles to contract violently; induces massive secretions by secretory cells; and depolarizes every excitable tissue investigated (Deguchi et al., 1976; Ito et al., 1977; Weidmann, 1977; Dubois and

Table 1
Occurrence of palytoxin and analogues in marine organisms.

Organisms	Locale	References
Zoantharians		
Palythoa caribeaorum	Jamaica	Attaway, 1968
Palythoa mammilosa	Jamaica	Attaway and Ciereszko, 1974
Palythoa tuberculosa	Okinawa	Hashimoto et al., 1969
Palythoa toxica	Hawaii	Moore and Scheuer, 1971
Palythoa vestitus	Hawaii	Quinn et al., 1974
Palythoa aff. *margaritae*	Japan	Oku et al., 2004
Zoanthus solanderi	Caribbean	Gleibs et al., 1995
Zoanthus sociatus	Caribbean	Gleibs et al., 1995
Dinoflagellates		
Ostreopsis lenticularis	Caribbean	Mercado et al., 1994
Ostreopsis siamensis	Okinawa	Usami et al., 1995
Ostreopsis mascarensis	Indian Ocean	Lenoir et al., 2004
Ostreopsis ovata	Italy	Ciminiello et al., 2006; 2008
Algae		
Chondria armata	Japan	Maeda et al., 1985
Sea anemone		
Radianthus macrodactylus	Seychelles	Mahnir et al., 1992
Polychaete worm		
Hermodice carumculata	Caribbean	Gleibs et al., 1995
Crabs		
Lophozosimus pictor	Singapore	Lau et al., 1993; 1995
Demania reynaudii	Philippines	Alcala et al., 1988
Platypodiella spectabilis	Caribbean	Gleibs et al., 1995
Fishes		
Alutera scripta (filefish)	Ryukyu	Hashimoto et al., 1969
Melichtys vidua (trigger fish)	Micronesia	Fukui et al., 1987
Ypsiscarus ovifrons (parrot fish)	Japan	Noguchi et al., 1987
Decapterus macrosoma (mackerel)	Philippines	Kodama et al., 1989
Herklotsichthys quadrimaculatus (sardine)	Madagascar	Onuma et al., 1999
Epinephelus sp.	Japan	Taniyama et al., 2002

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