

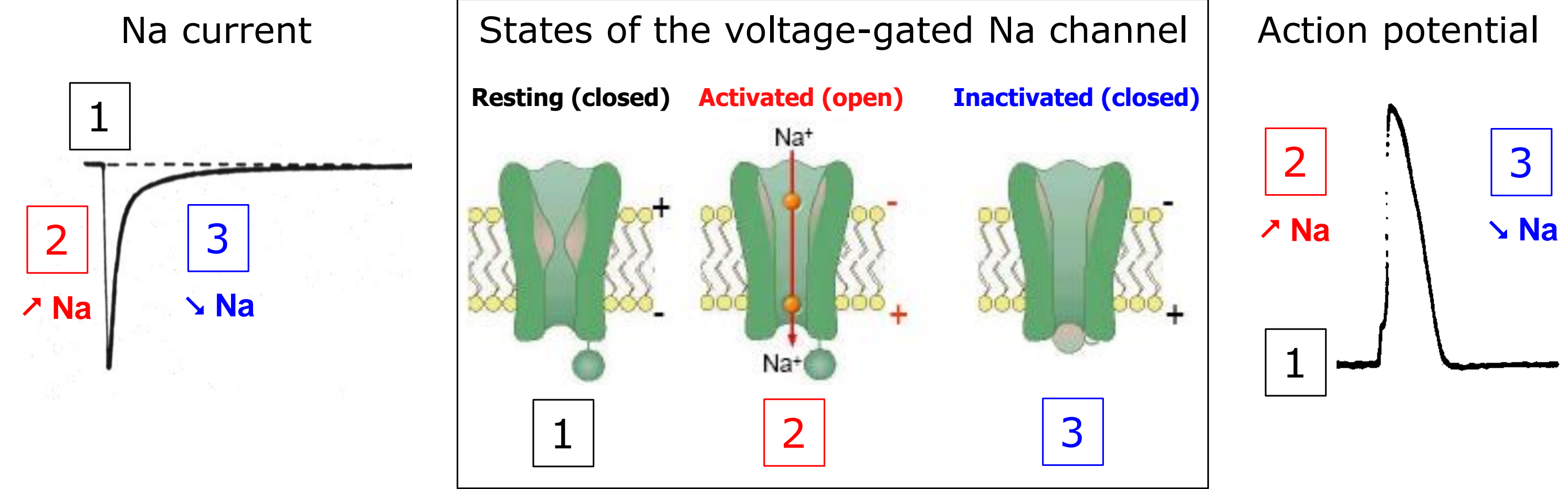
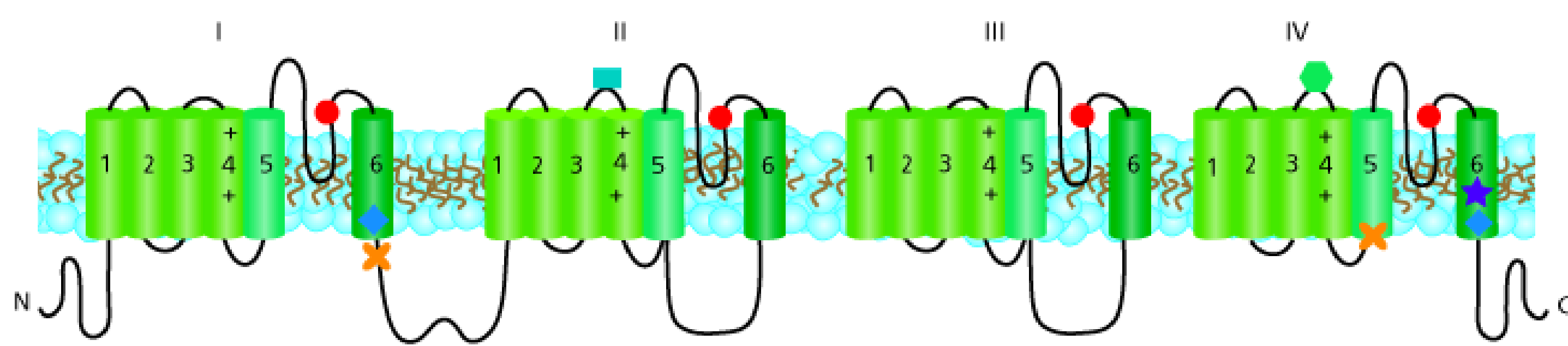
The voltage-dependent sodium channel : A well-known molecular target of saxitoxins (cyanotoxins), ciguatoxins and brevetoxins (phycotoxins)

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Structure and functioning of the voltage-dependent sodium channel

- ◆ veratridine, batrachotoxin, aconitine, grayanotoxin (persistent activation)
- α-scorpion toxin, β-pomplidotoxin, sea anemone toxin (prevent outward movement of voltage sensor)
- β-scorpion toxins (trap voltage sensor in outward position)
- tetrodotoxin, saxitoxin, μ-conotoxins (conductance inhibition)
- ★ local anesthetics (channel blockers)
- ✗ brevetoxins, ciguatoxins (persistent activation)



Because of its highly selectivity to Na ions, and activation (m) and inactivation (h) gating properties, the channel plays a fundamental role in the generation and conduction of action potentials. Starting from a resting state where it is closed, it rapidly **activates** (opens) as a function of time and membrane potential, giving rise to an inward current responsible for the ascending phase of the action potential (membrane depolarization), and then slowly **inactivates** (closes), giving rise to the current decay and thus, the return of membrane potential to its resting value.

The channel α-subunit is a transmembrane protein composed of 4 domains (DI-DIV), each of them consisting in 6 segments (S1-S6). The segment S4 is responsible for the channel activation and the P loop, connecting S5 and S6, is involved in the channel selectivity. Receptor-sites for toxins and local anaesthetics are identified on this α-subunit.

Sources of aquatic neurotoxins and responsive organisms

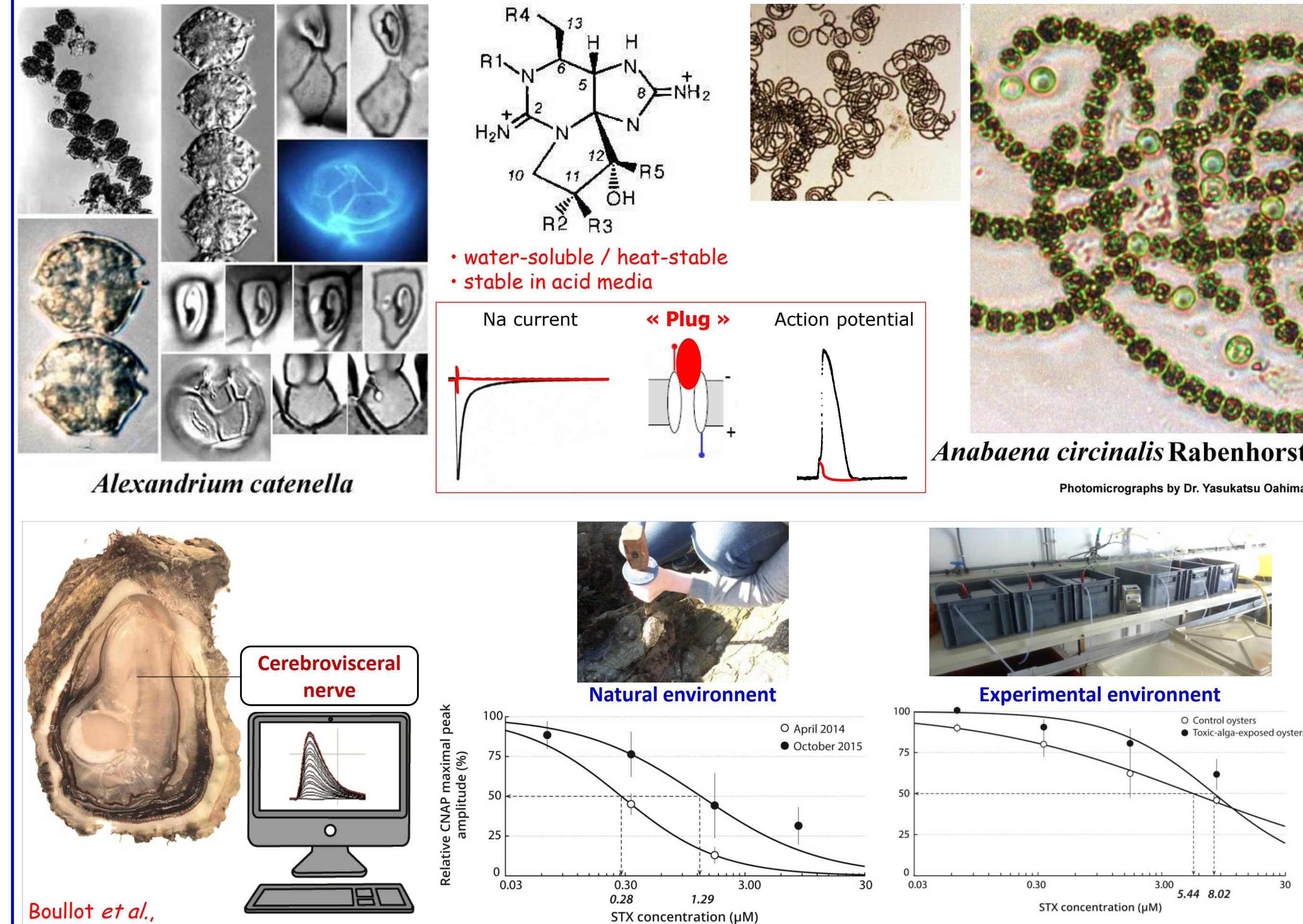
Intoxications

Organism Group	Organism	Toxin
Dinoflagellates	<i>Alexandrium sp.</i>	Saxitoxins, Neo-saxitoxins
	<i>Karenia selliformis</i>	Gymnodimines
	<i>Vulcanodinium rugosum</i>	Pinnatoxins
	<i>Alexandrium ostenfeldii</i>	Spirolides
	<i>Prorocentrum</i>	Prorocentrolides
	<i>Karenia brevis</i>	Brevetoxins
	<i>Protoperidinium</i>	Azaspiracids
	<i>Pseudonitzschia</i>	Domoic acid
	<i>Dinophysis</i>	Okadaic acid
	<i>Gambierdiscus toxicus</i>	Ciguatoxins
Bacteria	<i>Ostreopsis</i>	Maitotoxins, Gambierol, Palytoxins
	<i>Bacillus spp. (19 strains)</i>	Tetrodotoxins
Cyanobacteria	<i>Micrococcus</i>	
	<i>Acinetobacter</i>	
	<i>Microbacterium</i>	
	<i>Proteus</i>	Histamine
	<i>Klebsiella</i>	
	<i>Lactobacillus</i>	
Cyanobacteria	<i>Anabaena</i>	Anatoxin-a, Saxitoxins
	<i>Aphanizomenon</i>	Cylindrospermopsin, STX
	<i>Cylindrospermopsis</i>	Cylindrospermopsin, STX
	<i>Microcystis</i>	Microcystin
	<i>Nodularia</i>	Nodularin
	<i>Oscillatoria</i>	Anatoxin-a

Envenomations

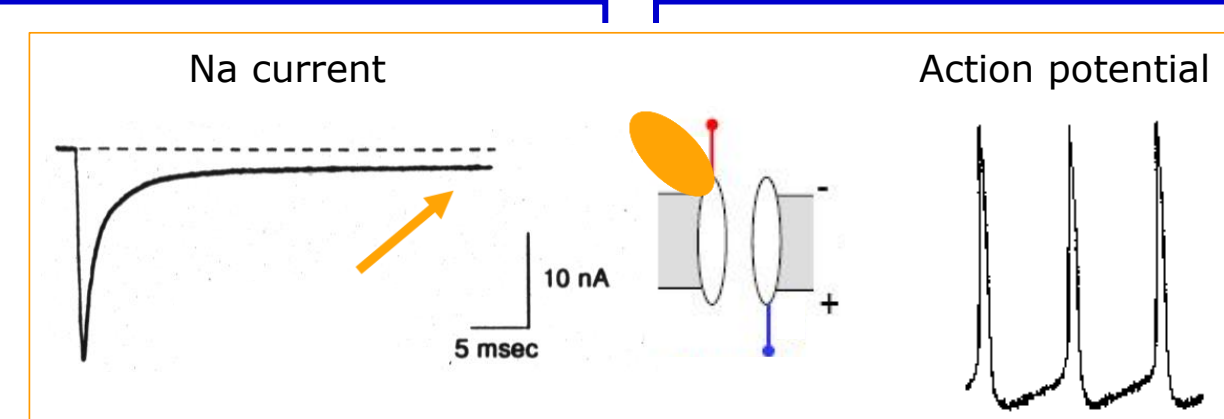
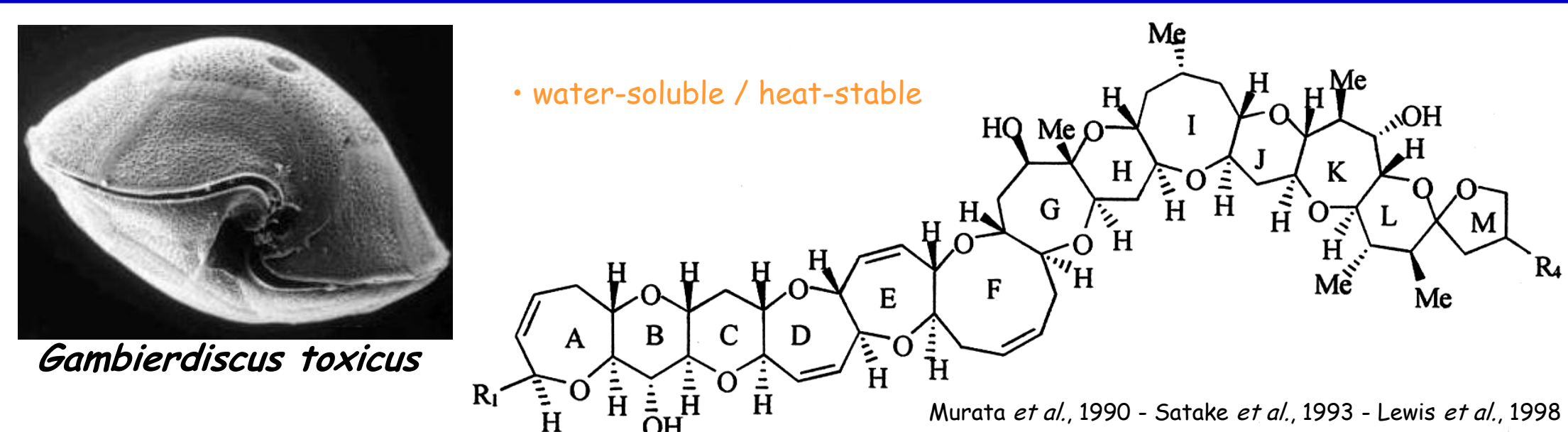
Organism Group	Organism	Toxin
Cnidaria	<i>Anemonia sulcata</i>	ATX
	<i>Stichodactyla heliantus</i>	ShK
	<i>Anthopleura elegantissima</i>	Sticholysins
	<i>Actinia equina</i>	APETx1
	<i>Actinia equina</i>	Equinatoxins
Mollusks	<i>Conus</i>	α-CTX, ψ-CTX, ι-CTX, ω-CTX, κ-CTX, μ-CTX, δ-CTX, χ-CTX, σ-CTX, Conantokins
	<i>Octopus macropus</i>	Cephalotoxin
Worms	<i>Glycera convoluta</i>	α-glycerotoxin
	<i>Lumbriconeria heteropoda</i>	Nereistoxin
Fish	<i>Synanceia trachynis</i>	Trachynylisin
	<i>Synanceia verrucosa</i>	Neo-verrucotoxin
	<i>Synanceia horrida</i>	Stonustoxin
Snake	<i>Laticauda semifasciata</i>	Erabutoxin, κ-neurotoxins

Saxitoxins, gonyautoxins and derivatives - Paralytic Shellfish Poisoning

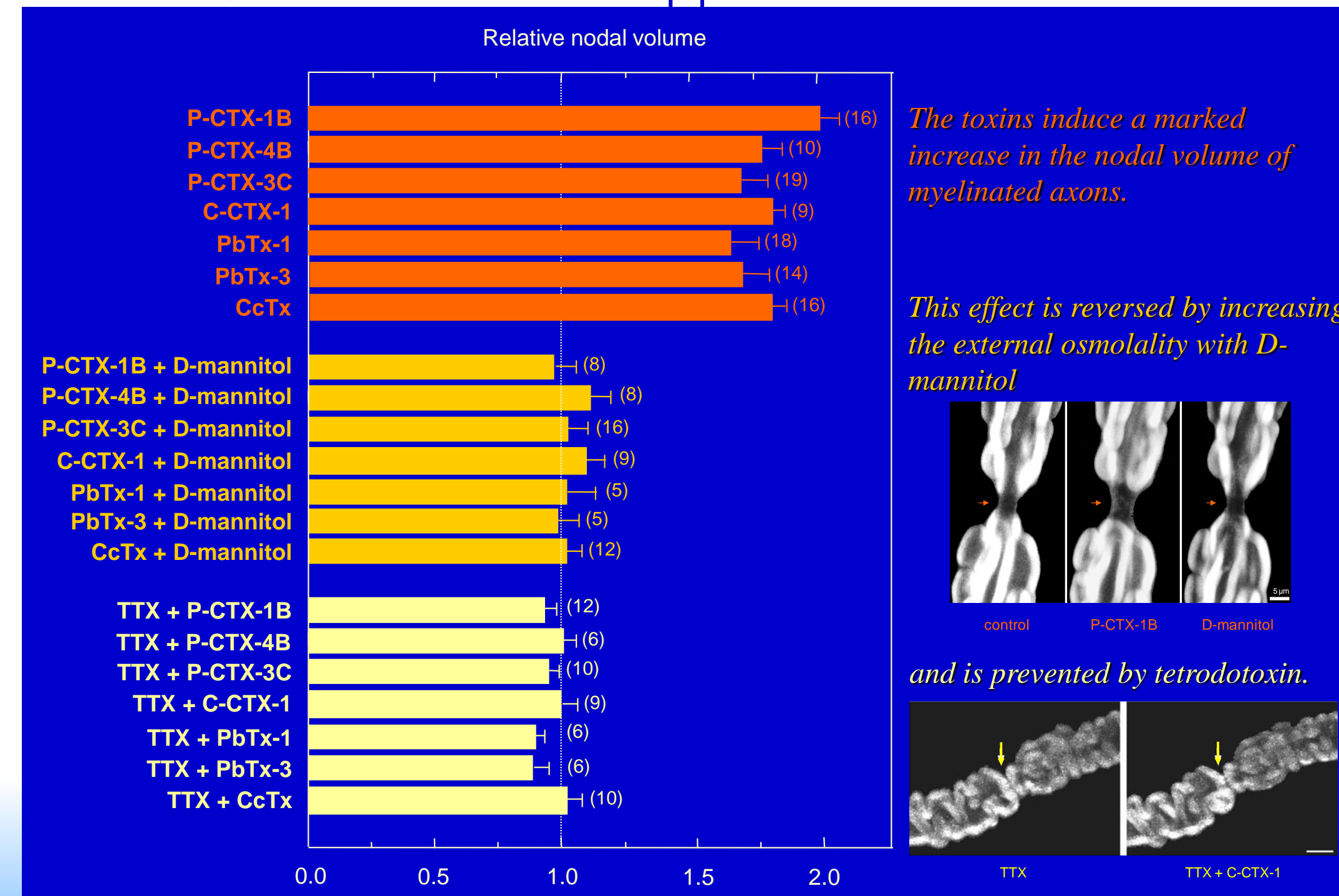
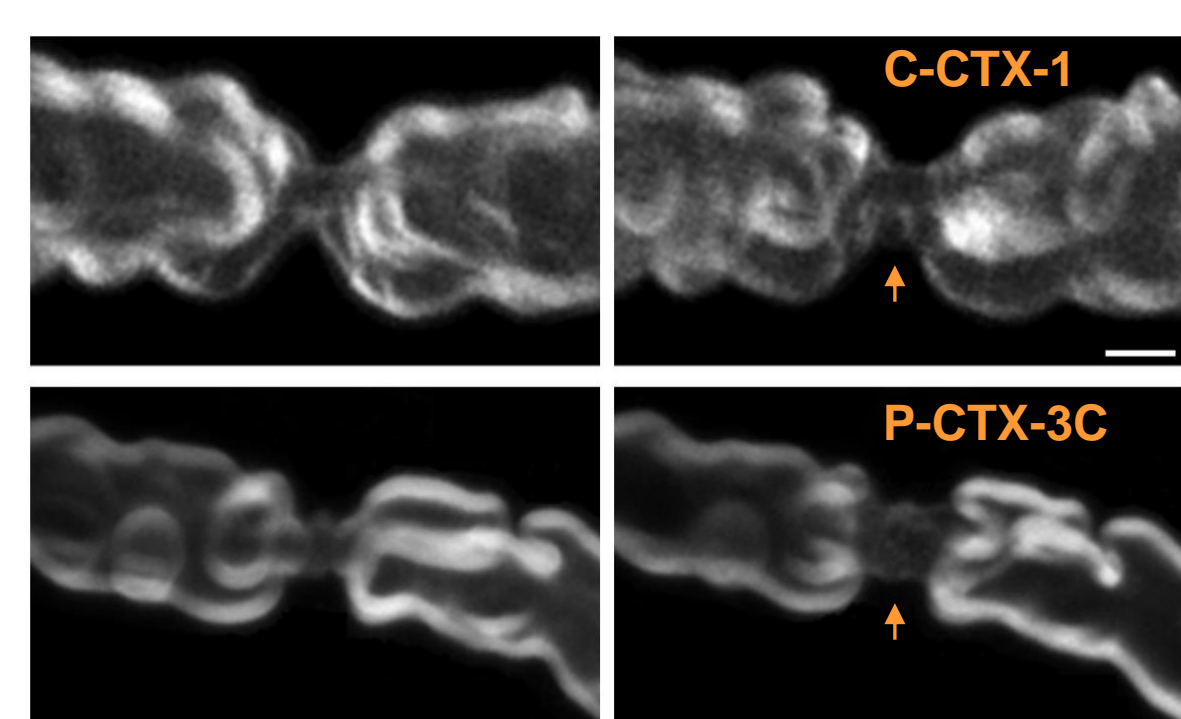
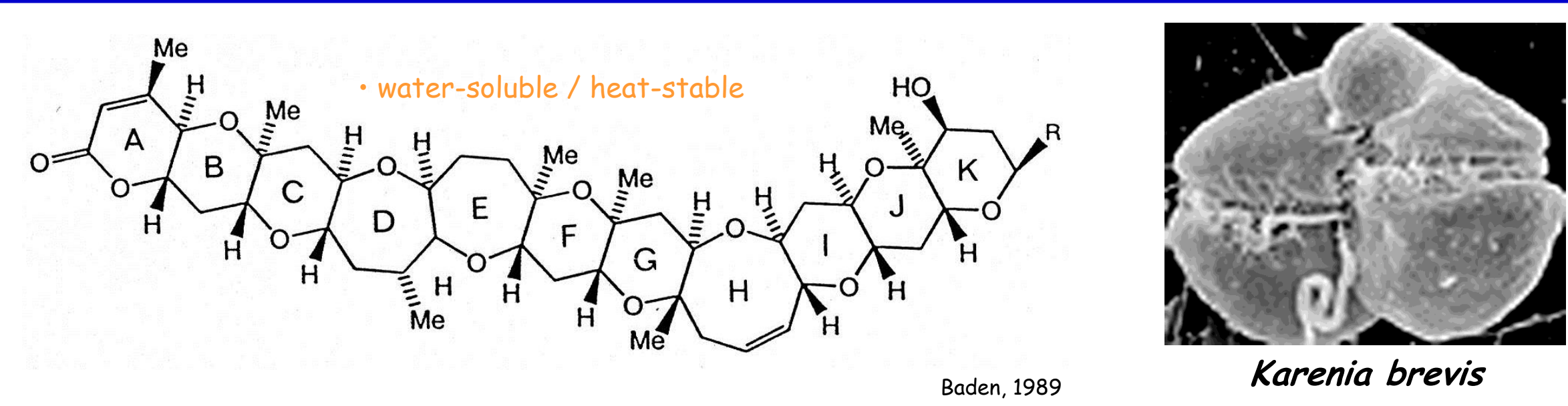


This family of divalent and tricyclic cations, produced by some dinoflagellates and cyanobacteria and responsible for PSP, interacts with the channel receptor-site 1, leading to pore blockade and thus to current and action potential inhibition. This is exemplified by an electrophysiological study of oyster cerebro-visceral nerve sensitivity to saxitoxin.

Ciguatoxins - Ciguatera Fish Poisoning



Brevetoxins - Neurologic Shellfish Poisoning



Mattei et al., J. Neurosci. Res., 1999, 55(6):666-673
Mattei et al., Neuropharmacology, 2014, 85:417-426

Consequently, toxin-induced cell swelling occurs. This is exemplified by confocal-imaging studies of toxin effects on vertebrate myelinated nerve fibers.

Ciguatoxins and brevetoxins, two families of cyclic polyethers produced by some dinoflagellates and responsible for CFP and NSP, respectively, interact with the receptor-site 5 of sodium channels, leading to partly blockade of inactivation and thus to spontaneous and/or repetitive action potentials.