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Molecular Basis of Voltage-Gated Sodium Channel Interaction with Marine Toxins Tetrodotoxin (TTX) from the Puffer Fish, Tetraodontidae

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Abstract

Tetrodotoxin (TTX) is one of the most potent neurotoxins known, which is an extremely potent low-molecular weight non-protein which is isolated from puffer fish at first. Poisoned people by TTX which can block sodium channels, will lead to limbs numbness, paralysis, even to die. TTX can relieve pain, mitigate and so on, so it is very important in clinically. In this paper, we review the Na_V structure , gene family and molecular mechanisms by which Na_V interacts with TTX, and adaptive changes in TTX-resistance and the possible consequences for Na_V biophysical properties.

Keywords: Tetrodotoxin; TTX; Sodium channel; Na_V; Puffer fish

Introduction

Tetrodotoxin (TTX) was first isolated from puffer fishes ,then named after the puffer fish family, Tetraodontidae [1]. It isolated in 1909 and chemically defined in 1964 Hanifin [2] Bane et al. [3] firstly and from now on over 20 species of puffer fish have been found to harbour the toxin [4]. TTX is a thermostable, low molecular weight and non-proteinaceous neurotoxin [5]. TTX is one of the best-known marine toxins because of its frequent involvement in fatal food poisoning and selectively binds to voltage-gated sodium channels (Na_V) in muscle and nerve tissues causing paralysis and death [6,7]. TTX has also been reported from Echinodermata (star fishes), Crustacea (crabs), Chordata (newts, frogs), Mollusca (gastropods, sea slugs, blue-ringed octopuses), Chaetognatha, Arthropoda, Platyhelminthes, Annelida and Algae (ribbon worms) [8].

The hypothesis origin of TTX

Matsui et al. [9] first brought the hypothesis exogenous origin of TTX what suggested that all TTX-bearing organisms were infected by TTX-producing microorganisms living symbiotically within their bodies [10,11]. This postulation was later confirmed by the isolation of TTX-producing bacteria from various TTX-bearing animals. The TTX accumulation mechanism of puffer fish has been assumed to consist not only of external food web-borne TTX produced by bacteria but also of TTX internally produced by their intestinal bacteria. Since other animals which are likely to eat the same diet as puffer fish do not become toxic, puffer fish are assumed to have special mechanism to retain TTX [12]. Thereafter, many studies have established a direct link between TTX (including TTX derivatives) and the presence of TTX-producing bacteria, and the number of TTX-producing bacteria strains have been increasing [13]. The first reported TTX-producing microorganism was *Vibrio* which isolated from the intestine of *xanthid* crab [14]. Wu et al. [15] reported 20 out of 36 isolated bacteria strains were found to produce TTX in vitro. Their results suggested that TTX-producing bacteria are closely related to the toxification of the puffer fish. And this is the first study in which TTX-producing *Bucillus* and *Actinomyces* were isolated from the toxic China Bohai Sea puffer fish *Fugu rubripes*. At least 150 bacterial strains are claimed to be TTX producers [16].

However, there are some arguments against the contribution of associative microflora to host organism intoxication. Detection of TTX-producing bacteria in marine and fresh water sediments allowed hypothesizing TTX bioaccumulation through small zooplankton and detritus feeders along the food chain [17]. *Vibrio alginolyticus* has been reported as a good producer of tetrodotoxin (TTX), but the toxin extracted from this bacterium did not react to the monoclonal antibody against TTX. Surprisingly, chromatographic analyses detected high TTX peaks for polypeptone and yeast extracts used as medium materials, which were, as expected, all negative through the mouse bioassay. These results may require us to revise the bacterial production of TTX [18,19]. In spite of numerous data on TTX-producing bacteria, the contribution of microorganisms to TTX bioaccumulation is still subject to debate in marine ecosystems [16].

Physicochemical property of TTX

TTX is a heterocyclic, organic perhydro quinozolineamine molecule (amino perhydro quinazolone). Its structure was elucidated by R. B. Woodward in 1964 [3]. The empirical formula of TTX is C11H17N3O8 [7]. TTX is water soluble , heat stable Bane et al. [3]and low molecular weight toxin (M.W. = 319.3) with extremely high potency (Human LD50 = 10.2 μg/kg) [2]. TTX possesses a unique cage-like structure [20]. Structurally TTX consists of a guanidinium moiety that is positively charged at physiological pH connected to a highly oxygenated carbon skeleton that possesses a 2,4-dioxaadamantane portion containing five hydroxyl groups Chau et al. [20], is essential for blocking the Na_v channels [7]. TTX co-exists with its naturally occurring analogues [3]. There have been 30 structural analogues of TTX reported (see review of Chau et al. [20] Bane [3] and the degree of toxicity varies with structure [21]. Many researchers have been intrigued as to how TTX bearing organisms are themselves resistant to the toxic effects of TTX. The reason is because the aromatic amino acid chain in the p-loop region of domain I in the sodium channels in these animals is replaced by a non-aromatic amino acid and this prevents the sodium channels in these species from being blocked [22,23] (Figure 1).

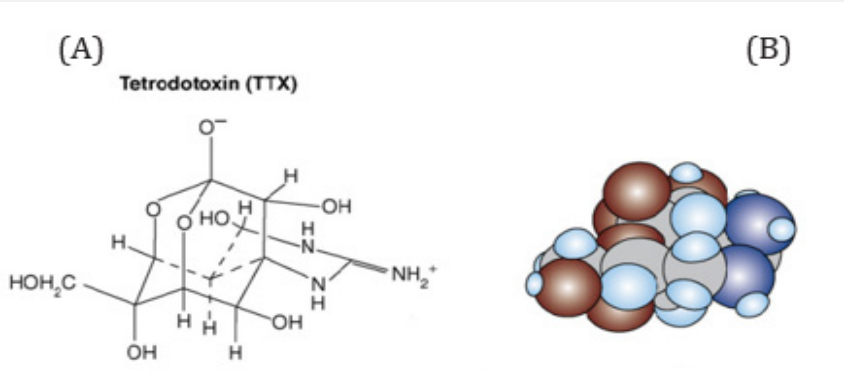

Figure 1: Molecular structures (A) and models (B) of tetrodotoxin [7].

Structure and function of Voltage-Gated Sodium Channels (Na_v)

The sodium channel is a membrane protein that mediates the voltage-dependent modulation of the sodium ion premeability of electrically excitable membranes [24,25]. Sodium currents were first recorded by Hodgkin and Huxley [26], who used voltage clamp techniques to demonstrate the three key features that have come to characterize the sodium channel: (1) voltage-dependent activation, (2) rapid inactivation, (3) selective ion conductance. Noda et al. [27] isolated cDNAs encoding the entire polypeptide from expression libraries of electroplax mRNA. Their work gave the initial insight into the primary structure of a voltage-gated ion channel. The primary structures of at least five distinct sodium channels (eel, rat brain, rabbit skeletal muscle). In human and rodents, ten Na_v channel genes have been cloned and classified into a single family. The gene names are Na_v 1.1 to Na_v 1.9, with the last gene of unknown function designated Na_x Soong et al. [7] and different members of Na_v isoforms are expressed in different types of excitable tissues [28].

A voltage-gated sodium (Na_v) channel comprises a pore-forming α-subunit (240-280 kDa) in association with one or more smaller accessory β-subunits (33~37 kDa) [28,29]. The β-subunits is a single trans-membrane structure with a large extra-cellular immunoglobulin-like domain. The auxiliary β-subunit are important in modifying voltage dependency and the kinetics [30]. In addition, they play important roles in cell adhesion, signal transduction and channel expression at the plasma membrane [31]. The α-subunit is important in channel function, including voltage sensitivity and ion selectivity [28]. The sodium channel α subunit has four homologous repeated domains (I-IV) with a circular radial arrangement in which a central ion pore is formed (Figure 2). This brings domains I and IV into close proximity. Each domain consists of six putative transmembrane helical segments (S1-S6) [32]. The most conserved segment is S4, present in each

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repeated domain, which contains a unique motif of a positively charged amino acid residue followed by two nonpolar residues that repeat four to eight times in each helix [33]. The S4 segment is the voltage sensor that responds to membrane depolarization to trigger the activation, or opening, of the channel enabling Na^+ ions to flow through the channel pore into the cell [7]. The pore is formed on the extracellular side by a narrow selectivity filter comprising four re-entrant P-loops situated between the S5 and S6 segments of the four domains. Specifific residues lining the P-loops of the selectivity filter preferentially permit the flow of Na^+ compared with K+ ions and other cations. On the inner side, the S5 and S6 segments line the wider part of the pore (or inner vestibule) that exits into the cytoplasmic side of the membrane [34]. As shown in Figure 2, the short segments SS1 and SS2, which are part of the extracellular amino acid loop between transmembrane segments S5 and S6, are supposed to form a hairpin structure inside the membrane and to serve as part of the ion-conductive pathway. The intramembrane short segment is referred to as the pore region.

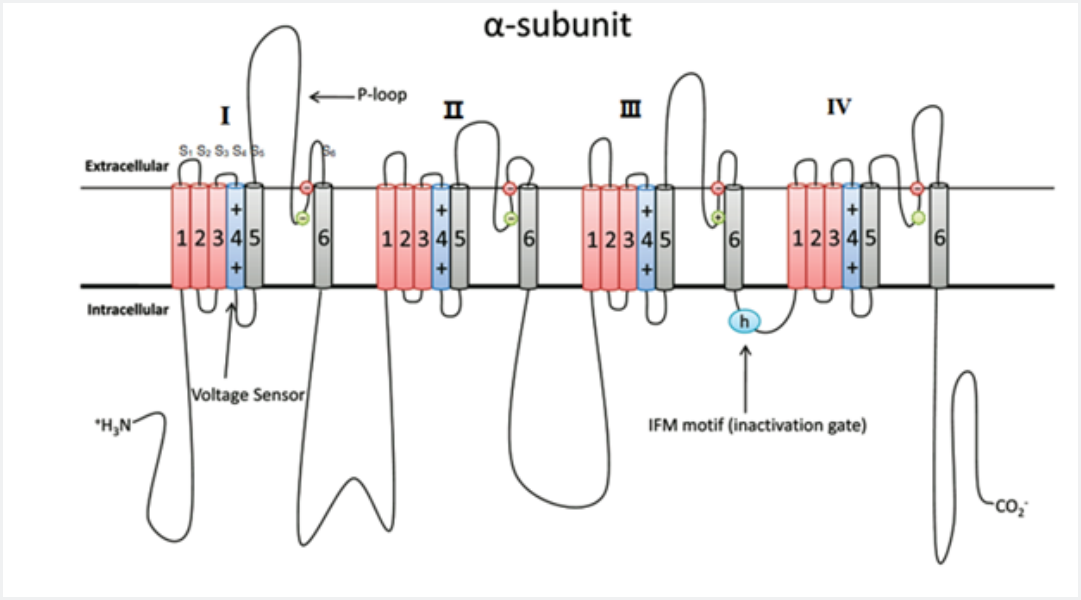

Figure 2: α-subunit of voltage-gated sodium channel. The S4 segments indicated by (+) are suggested to participate in the voltage sensing mechanism. The P-loop connecting domains III and IV is the region suggested to participate in the fast inactivation [28,33].

The huge influx of Na^+ ions into excitable cells, like muscles or neurons, initiates the generation and propagation of action potentials. The fast activation of the Na_v channels is coupled to fast inactivation, or closing, of the channel, which occurs over 1-2 ms. The inactivation gate is formed by the intracellular loop region between domains III and IV. The inactivation gate acts like a 'hinged-lid' and folds into the channel to occlude the pore from the intracellular side [35,36]. The Na_v channels therefore have crucial roles in electrical signaling in the nervous system and in excitation-contraction coupling in muscles [7].

The mechanism of toxification of TTX

Molecular cloning and expression of Na^+ channel cDNAs show multiple isoforms of Na^+ channels that are encoded by a multigene family in mammals, where a difference in primary structure accounts for the possession of TTX-S or TTX-R properties [37]. There are six sites on the channels to which toxins can bind, and the effects of toxin inhibition can be categorized according to their modes of action [38]. The non-peptides tetrodotoxin (TTX) that bind to site 1 in the extracellular surface of the channel to occlude the pore [39]. TTX is a sodium channel blocker and the mechanism of its toxicity has been investigated in animal models [40]. TTX blocks the Na^+ flow and suppresses the voltage potential between external and internal neuron cells at nanomolar concentrations [41,42]. Na_v of the puffer fish and newts have been reported to carry mutations in various sites of different channel isoforms [22]. Mutations in the channel can affect the rate of nerve impulse, sensory transduction and muscle contraction and therefore animals' fitness [28]. Predators of TTX-carrying organisms have co-evolved to become TTX-resistant via mutations in Na_v, allowing them to consume tetrodotoxic prey [43,44].

TTX is bound to each SS2 region of repeats I, II, III and IV. Especially two negatively-charged amino acids in SS2 regions of repeats I (Asp-384, Glu-387) and II (two Glu-942), one positively charged amino acid in SS2 region of repeat III (Lys) and one negatively-charged amino acid in SS2 region of repeat IV (Asp) have been identifified as major determinants of toxin sensitivity [22,45]. According to the mutagenesis carried out by Terlau et

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al. [46], the TTX binding site exists in SS2 region, locating in the highly conserved pore-forming region (P-loop) between the fifth and the sixth transmembrane segments (S5-S6) in each domains I-IV [46]. The TTX binding site was mainly investigated by site-directed mutagenesis [47]. All these data agree and suggest that the sensitivity to TTX is markedly influenced by a single amino acid displacement of aromatic residue with non-aromatic one at the same position in SS2 region (Table 1).

Table 1: Mutations in the Nav channel.

Species	Tissue	Nav channel	Mutation	IC50-TTX value changed	Reference
Rat	innervated skeletal muscle	TTX-sensitive	Tyr to Cys	16 nM to more than 50 mM	Backx et al. [48]
	brain II	TTX-sensitive	Phe to Cys	18 nM to more than 10 mM	Heinemann et al. [49]
	innervated skeletal muscle	TTX-sensitive	Cys to Tyr	3 mM to 8 nM	Chen et al. [50]
	denervated skeletal muscle	TTX-resistant	Tyr to Cys	35 nM to 1 mM	
	heart	TTX-sensitive	Arg377 to Asn	did not alter the sensitivity to TTX	Satin et al. [51]
			Cys374 to Tyr	950 nM to 1.3 nM	
	Sensory neurons	TTX-resistant	Ser to Cys	≥ 100 mM	Akopian et al. [52], Sangameswaran et al. [53]
	sensory neuron	TTX-sensitive	Phe to Ser	60 mM to 2.8 nM	Sivilotti et al. [54]

TTX sensitivity of Na_v channels is decided by whether amino acid is aromatic or not in this region but TTX-tolerant species may have another way to change the affifinity of Na_v channel to TTX [22]. Various other amino acid substitutions in the pore region that confer TTX-resistance have also been reported in different species of puffer fish (Table 2) [60-73].

Table 2: Amino acid replacements is responsible for TTX resistance.

Species	Tissue	Sodium	Region	Mutation	References
Mammal	cardiac	Nav1.5	Domain I	Tyr-374-Cys	Satin et al. [51]
Cynops pyrrhogaster	Retinal neuronal	nRNaCh	Domain I	Ala to Phe or Tyr	Kaneko et al. [22]
Mice	nervous system	$Na_v1.8$, $Na_v1.9$	Domain I	Tyr-374-Cys	Cummins et al. [55]
Fugu pardalis *Takifugu rubripes* *Tetraodon nigroviridis* *Arothron nigropunctatus*	skeletal muscle	$Na_V1.4a$, $Na_V1.1La$, $Na_V1.5La$, $Na_V1.5Lb$ and $Na_V1.6b$	Domain I	Asn-401-Phe or Tyr	Yotsu Y et al. [45] Venkatesh et al. [56]
Softshell clams (Mya arenaria)		$Na_v1.4b$	Domain II	Glu-Asp	Bricelj et al. [44]
Rat	skeletal muscle	$Na_v1.4$	Domain III	Thr- Ile, Asp, or Lys	Choudhary et al. [57]
Mammal	skeletal muscle neural tissues	$Na_v1.1La$, $Na_v1.1Lb$, $Na_v1.4a$, $Na_v1.4b$, and $Na_v1.5Lb$	Domain III	Met-Thr	Terlau et al. [46]
Hirudo medicinalis	Nerve cords	Leech Na Channel	Domain III	Met-Thr	Blackshaw et al. [58]
Bdelloura candida		BdNa1	Domain IV	Ala-Gly	Jeziorski et al. [59]
T. sirtalis	skeletal muscle	$Na_v1.4$	Domain IV	Asp-to-Asn	Geffeney et al. [43]

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Conclusion

How is sodium channel function affected by the amino substitutions that impart TTX resistance? This question is being addressed by our present investigations into sodium channel function in chimeric channels carrying the amino acid substitutions that confer TTX resistance. Since the pore region is associated with channel gating and selectivity, and since the amino acid substitutions are predicted to alter channel structure sufficiently to impair TTX binding, it seems reasonable to speculate that selectivity, permeability and gating may be similarly affected. Our present experiments are designed to test this idea. The answers to this question will help us understand whether there are biophysical, and perhaps organismal, tradeoffs for the advantage of resistance to TTX.

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