河豚毒素生态作用研究进展

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摘要：河豚毒素（tetrodotoxin，TTX）取名于河豚鱼，最早从河豚鱼中分离纯化。自 1964 年河豚毒素化学结构被阐明以后，河豚毒素研究得到了生物学家、毒理学家、化学家、药理学家的广泛关注。河豚毒素具有许多天然同系物。河豚毒素及其同系物在自然界分布广泛，存在于一系列不同进化水平的海洋生物和少量的两栖动物体内。河豚毒素及其同系物可能具有防御、捕食及信息传递等生态作用，毒素在生物体内的分布与其生态作用密切相关。含有河豚毒素的生物对河豚毒素具有一定的耐受能力，其机制可能与生物体内存在河豚毒素结合蛋白或生物自身具有独特的钠离子通道结构有关。重点针对河豚毒素的生态作用及生物对河豚毒素的耐受机制进行了综述，以期为河豚毒素生态学研究及河豚毒素中毒事件的防范提供科学资料。

关键词：河豚毒素；分布；生态作用
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Advances in studies on the ecological roles of tetrodotoxin

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Abstract：Tetrodotoxin (TTX)，which was named after the puffer family Tetraodontidae，was first isolated from pufferfish in the 1950s. The structure of TTX was determined in 1964，since then TTX studies have attracted wide attentions from biologists，toxicologists，chemists and pharmacologists. TTX and many of its naturally-occurring analogues have been found in a range of marine organisms and in a few amphibians. It has been suggested that TTX and its analogues probably play a role in defense，predation or communication，and the tissue distribution of the toxins in TTX-bearing animals is highly relevant to its potential ecological roles. TTX-bearing animals show high resistance to TTX and its analogues，which is possibly due to the presence in these animals of TTX-binding proteins or uniquely-structured sodium-ion channels. This article reviews recent advances in the studies on the ecological roles of TTX，the resistance mechanisms of TTX-bearing organisms，and the prevention of TTX-poisoning.

Key Words：tetrodotoxin；distribution；ecological role

根据已有的记载，古埃及人最早发现了有毒的河豚鱼，在古埃及第五王朝（约公元前 2500 年）的贵族坟墓中有类似河豚鱼（*Tetraodon lineatus*）的图形。在中国和日本，大约 2000 年前就有关于食用河豚中毒的记载。1889 年，日本学者开始研究河豚鱼体内毒素的理化特性，而后，河豚鱼体内的毒素被命名为河豚毒素（tetrodotoxin，TTX）。到 1964 年，河豚毒素的分子式（$C_{11}H_{17}N_3O_8$）及其化学结构得以确定[1]。自此，河豚毒

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素研究得到了生物学家、毒理学家、化学家和药理学家的广泛关注,逐步阐明了河豚毒素的理化特征及毒性作用机制。目前,对于河豚毒素在生物中的分布与来源、化学特征、分析检测方法、中毒与治疗、药理学作用等方面都已有相关的综述[2]。为了更好地开展河豚毒素的生态学研究,拓展河豚毒素的应用领域,为河豚毒素中毒事件的防范提供思路,本文从河豚毒素的分布特征出发,对河豚毒素的生态作用和生物对河豚毒素的耐受机制进行了综述。

1 河豚毒素在生物中的分布

在很长一段时间里,河豚毒素被认为是河豚鱼中特有的一种有毒物质。直到 1964 年,蝾螈(*Taricha torosa*)体内的毒素也被确定为河豚毒素[1],才改变了这种看法。随后的研究表明,河豚毒素存在于一系列不同进化水平的海洋生物和少量的两栖动物体内。目前在细菌和放线菌[3~7],甲藻、红藻、扁形动物门、纽形动物门、软体动物门、环节动物门、节肢动物门、棘皮动物门、脊索动物门、毛颚动物门中的许多生物中都曾检测到河豚毒素(表 1)[2]。

表 1 含河豚毒素的生物

Table 1 Tetrodotoxin-containing organisms

分类 Classification		含河豚毒素的生物 Tetrodotoxin-containing organisms
甲藻 Pyrrophyta		塔玛亚历山大藻 *Alexandrium tamarense*
红藻 Rhodophyta		石灰质红藻 *Jania* sp.
扁形动物门 Platyhelminthes		海底平涡虫 *Planocera multitentaculata* and *P. reticulata*
纽形动物门 Nemertea		纽虫 *Lineus fuscoviridis*, *Tubulanus punctatus* and *Cephalothrix linearis*
软体动物门 Mollusca	腹足纲 Gastropoda	织纹螺科 Nassariidae *Zeuxis siquizorensis* and *Niotha clathrata*; Nassariidae *Zeuxis scalaris* and *Z. castus*-like specimens[8]; *Nassarius succinctus* and *Nassarius semiplicatus*[9] 玉螺科 Naticidae Lined moon shell *Natica lineate*, Calf moon shell *Natica vitellus* and bladder moon shell *Polinices didyma*; pearshaped moon shell *P. tumidus*[10]; *Umborium suturale* and *Natica. pseustes*[11] 骨螺科 Muricidae *Rapana rapiformis* and *R. Venosa* 榧螺科 Olividae *Oliva miniacea*, *O. nirasei* and *O. Mustelina*[12] 峨螺科 Buccinidae *Babylonia japonica* 法螺科 Ranellidae *Charonia sauliae* 蛙螺科 Bursidae frog shell *Tutufa lissostoma*
	头足纲 Cephalopoda	章鱼科 Octopodidae *Hapalochlaena maculosa*
节肢动物门 Arthropoda	甲壳纲 Crustacea	扇蟹科 Xanthoidea *Atergatis floridus*, *Demania reynaudi*, *Lophozozymus pictor* and *Atergatopsis germaaini*; *Zosimus aeneus*, *Xanthias lividus*, *Actaeodes tomentosus*[13]; *Demania cultripes*, *Demania toxica*, *Lophozozymus incisus*[14] 蜘蛛蟹科 Majidae *Camposcia retusa*[14] 桡足类 *Pseudocaligus fugu* and *Taeniacanthus* sp. [15]
	肢口纲 Merostomata	鲎科 Limulidae horseshoe crab *Carcinoscorpius rotundicauda*
毛颚动物门 Chaetognatha		矢虫纲,箭虫科 Sagittoidea, Sagittidae *Eukrohnia hamata*, *Parasagitta elegans*, *Flaccisagitta scrippsae*, *F. Enflata* and *Spadella angulata*; *Aidanosagitta crassa*[16]
环节动物门 Annelida		缨虫 *Pseudopotamilla occelatus*
棘皮动物门 Echinodermata		海星纲 Asteroidea *Astropecten latespinosus*, *A. polyacanthus* and *A. scoparius*

续表

分类 Classification		含河豚毒素的生物 Tetrodotoxin-containing organisms
脊索动物门 Chordata	鱼纲, 鲀形目 Pisces, Tetraodontiformes	四齿鲀科 Tetraodontidae 叉鼻鲀属 *Arothron mappa*, *A. manilensis*, *A. nigropunctatus*, *A. hispidus*, *A. stellatus*, *A. reticularis* and *Chelonodon patoca* 圆鲀属 *Sphoeroides annulatus*, *S. lispus*, *S. lobatus*[17] 尖鼻鲀 *Canthigaster punctatissima*[17] 兔头鲀属 *Lagocephalus lunaris*[18] 多纪鲀属 *Takifugu pardalis* and *Takifugu poecilonotus* 凶兔头鲀 *Pleuranacanthus sceleratus*[19] 东方鲀属 *Fugu niphobles* 鲀属 *Tetraodon fangi*[20]; *Tetraodon steindachnericon*[21]
	鱼纲, 鲈形目 Pisces, Perciformes	鰕虎鱼科 Gobiidae *Gobius criniger*, *Yongeichthys nebulosus* and *Sillago japonica*; *Prachaeturichtys palynema* and *Radigobius caninus*[22]
	两栖纲,有尾目 Amphibia, Caudata	蝾螈科 Salamandridae *Taricha torosa*, *T. granulosa*, *Notopthalrnus viridescens*, *Cynops pyrrhogaster*, *C. ensicauda*, *Triturus vulgaris*, *Notophthalrnus viridescens*, *Triturus oregon*, *Triturus vulgaris*, *Ambystoma tigrinum*, *Taricha granulose* and *Paramesotriton hongkonggensis*; *T. rivularis*, *T. cristatus*, *T. alpestris*, *T. marmoratus*[23]; *Triturus alpestris*[24]
	两栖纲,无尾目 Amphibia, Apoda	蟾蜍科 Bufonidae *Atelopus varius* (*A. varius varius*), *Atelopus varius* (*A. varius ambulatorius*), *Atelopus chiriquiensis* and *Atelopus oxyhynchus*; *Atelopus varius* (*A. varius zeteki*)[25]; *Atelopus spumarius*, *A. varius*, *A. spurrelli*, *A. ignescens* and *A. zeteki*[26]; *Atelopus subornatus* and *A. peruensis*[27] 短头蟾科 Brachycephalidae *Brachycephalus ephippium*; *Brachycephalus pernix*[28] 箭毒蛙科 Dendrobatidae *Colostethus inguinalis* 树蛙科 Rhacophoridae *Polypedates* sp.

2 河豚毒素的同系物

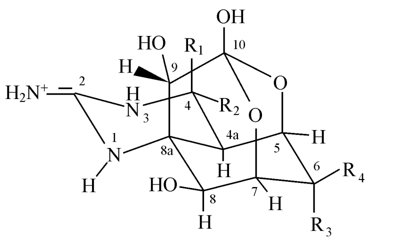
在河豚鱼中,河豚毒素与其同系物是同时存在的[29]。河豚毒素的同系物种类较多,目前从河豚、纽虫、两栖类等生物体内分离得到的同系物包括:4-*epi*TTX,6-*epi*TTX,11-deoxyTTX,11-deoxy-4-*epi*TTX,11-norTTX-6(R)-ol,11-norTTX-6(S)-ol,11-norTTX-6,6-diol,4, 9-anhydroTTX,11-oxoTTX,4,9-anhydro-4-*epi*TTX,4,9-anhydro-11-deoxyTTX,5-deoxyTTX,tetrodonic acid [2],4,9-anhydro-6-*epi*-TTX [30]、5,6,11-trideoxyTTX [31]、4-CysTTX [32]等,河豚毒素及其同系物的化学结构如图 1 所示[9]。这些同系物可能与河豚毒素的代谢或生物合成有关[33, 34]。在河豚毒素的同系物中,5-deoxyTTX、5,6,11-trideoxyTTX、4-CysTTX、4,9-anhydroTTX、4,9-anhydro-6-*epi*-TTX、河豚酸等同系物的毒性较低,甚至无毒[30, 35],而 11-oxoTTX 虽比较罕见,其毒性却是 TTX 的 4 ~5 倍[36]。

3 河豚毒素的生态作用

河豚毒素及其同系物在生物界有如此广泛的分布,说明河豚毒素可能具有重要的生态作用。在含有河豚毒素的生物中,河豚毒素主要分布在生物的体表或消化道、肝脏、卵巢等内脏中,而蓝纹章鱼(*Hapalochlaena maculosa*)[37]和毛颚类动物[16]能够产生含有 TTX 的毒液。河豚毒素在生物体的分布位置与其生态作用密切相关。

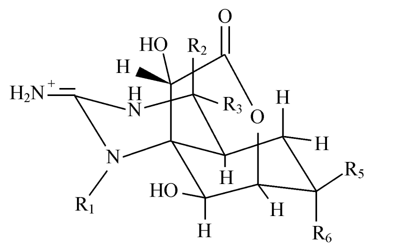
分布于生物体表或者体内的河豚毒素具有重要的保护作用,可以警示或威慑其捕食者。在四齿鲀科(Tetraodontidae)的河豚鱼体表和粘液中能够检测到河豚毒素,纽虫(*Cephalothrix linearis*)[38]和蝾螈(*Taricha* sp.)、树蛙(*Polypedates* sp.)、短头蟾(*Brachycephalus ephippium*)等两栖动物中也有体表分泌毒素的现象[23, 39, 40]。在对 9 种蝾螈的研究中发现,在雄性蝾螈中,TTX 及其同系物在皮肤中的含量最高,而在雌性蝾螈的卵巢中含量最高,其它组织中 TTX 含量均较低[24]。TTX 及其同系物在动物皮肤和卵巢中的集中分布说

明 TTX 可能具有警示捕食者的作用。在对美国粗皮蝾螈(*Taricha granulosa*)研究中发现,经过长期的自然选择,这种蝾螈与其捕食者束带蛇(*Thamnophis sirtalis*)之间产生了明显的协同进化现象。体内不含 TTX 的蝾螈与对 TTX 不具备耐受力的蛇的分布区有重叠,而在对 TTX 有较高耐受力的蛇的活动区域,蝾螈体内也含有较高含量的 TTX。由此可以说明,河豚毒素对于粗皮蝾螈防御捕食者具有重要作用[30]。Pires 等在对两栖类的研究中发现,在含有河豚毒素的无尾目两栖动物中,动物体表的鲜亮色彩与其体内的毒素含量存在一定的关系。带有明亮警戒色的短头蟾属和斑蟾属的一些种类,其体内的毒素含量更高。这表明警戒色可以作为其体内河豚毒素的广告,对捕食者产生威慑作用[36]。动物的卵和幼体比较容易受到捕食者的侵害,也有少量动物能够产生带有河豚毒素的卵。在蝾螈(*Taricha torosa*)[1]、蛙(*Atelopus chiriquiensis*)[41]、蓝纹章鱼(*Hapalochlaena maculosa*)[37]、扁虫(*Planocerid* sp.)[42]等动物的卵中都曾检测到 TTX。在东美螈(*Notophthalmus viridescens*)的幼体阶段体内也含有 TTX[43]。



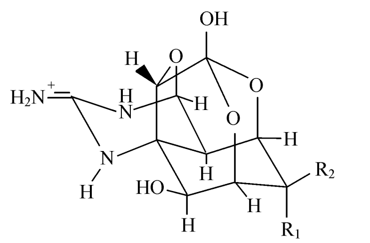
a

毒素名称 Toxins	R1	R2	R3	R4
TTX	H	OH	OH	CH_2OH
4-epiTTX	OH	H	OH	CH_2OH
6-epiTTX	H	OH	CH_2OH	OH
11-deoxyTTX	H	OH	OH	CH_3
4-epi-11-deoxyTTX	OH	H	OH	CH_3
11-norTTX-6(S)-ol	H	OH	OH	H
11-norTTX-6(R)-ol	H	OH	H	OH
11-norTTX-6,6-diol	H	OH	OH	OH
11-oxo-TTX	H	OH	OH	CH(OH)2



b

毒素名称 Toxins	R1	R2	R3	R4	R5
5-deoxyTTX	H	H	OH	OH	CH_2OH
5,11-dideoxyTTX	H	H	OH	OH	CH_3
6-epi-5,11-dideoxyTTX	H	OH	H	OH	CH_3
1-hydroxy-5,11-dideoxyTTX	OH	OH	H	OH	CH_3
5,6,11-trideoxyTTX	H	H	OH	H	CH_3
4-epi-5,6,11-trideoxyTTX	H	OH	H	H	CH_3



c

毒素名称 Toxins	R1	R2
4,9-anhydroTTX	OH	CH_2OH
4,9-anhydro-6-epiTTX	CH_2OH	OH
4,9-anhydro-11-deoxyTTX	OH	CH_3

图 1 河豚毒素及其同系物的化学结构

Fig. 1 Structures of tetrodotoxin and its analogues

a. 半醛糖型毒素同系物 Hemilactal type TTX analogues; b. 内酯型毒素同系物 Lactone type analogues; c. 4,9 脱水型毒素同系物 4,9-anhydro type TTX analogs

一些动物中的河豚毒素能够在其捕食过程中发挥作用。蓝纹章鱼(*Hapalochlaena maculosa*) 和几种含毒的毛颚动物(Chaetognath)能够分泌含有 TTX 的毒液,分泌毒液的腺体分别位于章鱼和箭虫的后鳃腺和口中的乳突中,在咬食物的同时,毒液就会进入被捕食的生物体内,将其麻痹[16, 44]。在线纽虫(*Cephalothrix linearis*)和扁虫(*Planocerid* sp.)中,河豚毒素及其同系物在其摄食器官中的含量均较高[38, 42]。实验发现[42],扁虫在捕捉到猎物后体内 TTX 和 11-norTTX-6(S)-ol 的含量会下降,这为证实河豚毒素在捕食过程中的作用提供了直接证据。此外,含河豚毒素的生物本身对毒素具有一定的耐受性,这也使得它们在摄食其它含有河

豚毒素的生物时具有更高的竞争力[45]。

除上述两方面的作用之外,河豚毒素还具有其它生态学作用。曾有报道河豚毒素可以作为性信息素,在河豚鱼(*Fugu niphobles*)的产卵季节起到吸引雄性的作用。伴随着卵巢的成熟,大量河豚毒素在其卵母细胞中积累,在排卵过程中,这些河豚毒素就会从卵母细胞中释放出来,而成熟的雄性河豚鱼能够感受到 1.5 ~ 15 pM 的河豚毒素,这会诱导雄性河豚鱼赶来,从而提高其受精、繁殖的成功率[46]。在对 8 种含河豚毒素的腹足类软体动物进行实验时发现,有毒腹足类软体动物对 TTX 有一定的趋性,河豚毒素含量越高的腹足类软体动物,对 TTX 的趋性越明显[47]。在对寄生性的桡足类鱼蚤 *Pseudocaligus fugu* 和 *Taeniacanthus* sp. 的研究中发现,其体内存在 TTX,而且这两种寄生虫只存在于有毒河豚鱼的体表,这表明河豚毒素有可能是导致这种宿主专一性的重要原因[15]。此外,还有研究认为河豚毒素具有增强河豚鱼免疫力的作用[48]。

4　生物对河豚毒素的耐受作用及其机制

河豚毒素是海洋神经性毒素,对钠离子通道的选择性极高。河豚毒素与钠离子通道结合后,阻止钠离子进入细胞,从而阻断神经和肌肉产生兴奋活动,引起麻痹,严重时出现呼吸困难而导致生物死亡[49]。

含河豚毒素的生物不会因为其体内的毒素而中毒,对河豚毒素具有一定的耐受能力。腹腔注射河豚毒素,有毒河豚鱼对毒素的耐受力比小鼠高 300 ~ 750 倍,而无毒的河豚鱼对河豚毒素的耐受力仅是小鼠的 13 ~ 15 倍[50]。含有河豚毒素的铜铸熟若蟹(*Zosimus aeneus*)和花纹爱洁蟹(*Atergatis floridus*)对河豚毒素的耐受力也远高于无毒种类[51, 52]。

有学者认为,河豚毒素在生物体内能够与特定的蛋白结合,从而降低其毒性效应,这是生物对河豚毒素产生耐受能力的原因之一[53]。已有的实验发现,给无毒的河豚鱼投喂含河豚毒素的饲料后就很容易使河豚鱼累积毒素,但是,给其它的一些无毒鱼类,如竹荚鱼、真鲷和石鲷等投喂含河豚毒素的饲料,却未能观察到它们对河豚毒素的明显的积累[54]。在用河豚鱼肝脏切片的体外实验中发现,两种河豚鱼的肝脏都能够从水溶液中富集河豚毒素,而高毒性的豹纹多纪鲀(*Takifugu Pardalis*)肝脏切片对河豚毒素的富集能力显著高于低毒性的红鳍多纪鲀(*Takifugu rubripes*)[55]。这说明河豚鱼体内存在特有的截留河豚毒素的机制[56, 57]。有研究者从河豚鱼的血浆中纯化得到 TTX 结合蛋白并对其性质进行了研究[58, 59]。除河豚鱼之外,其它一些含有河豚毒素的生物体内也有类似的研究结果。研究发现,从含河豚毒素的扇蟹 (*Hemigrapsus sanguineus*) 体液中提取的蛋白能够中和具有致死效应的 TTX [60, 61]。目前对于 TTX 结合蛋白的特征还不是非常了解,但通常认为它们在含毒生物对毒素的耐受或毒素的积累过程中发挥一定的作用。

一些生物对河豚毒素的耐受性与其独特的钠离子通道结构有关。研究发现,3×10^{-6} M 的河豚毒素对 *Arothron hispidus* 等 7 种河豚鱼肌肉的动作电位没有影响,而 3×10^{-7} M 的河豚毒素却阻断了 3 种不含河豚毒素的其他鱼的动作电位[62]。河豚毒素的结合位点位于钠离子通道内高度保守的成孔区域(P-loop),对河豚毒素敏感的钠离子通道(TTX-sensitive Na^+ channel)在该区域有与 TTX 高度亲和的芳香性氨基酸。如果该区出现由芳香性氨基酸向非芳香性氨基酸的氨基酸置换,就会显著影响其与 TTX 结合的灵敏度,从而使钠离子通道成为抗河豚毒素的钠离子通道 (TTX-resistant Na^+ channel)[63]。通过对河豚鱼(*Fugu pardalis*)骨骼肌 Nav1.4 通道的 cDNA 基因序列图谱的研究发现,通道的结构域 I 的成孔区域的 401 位置包含有一个非芳香氨基酸,即天冬酰胺酸,而此位点发生的氨基酸置换可能与河豚鱼对高浓度的 TTX 耐受有关[64]。在捕食与防御的长期进化过程中,在北美西部,一些束带蛇对河豚毒素也具备了一定的耐受力,而且,不同地区的束带蛇对河豚毒素的耐受力也有明显差异。对这些束带蛇的 Nav1.4 通道进行分析发现,他们的芳香氨基酸在 401 位点是保守的,但在结构域 IV 的成孔区域发生了几处氨基酸置换。在 Willow Creek 地区的束带蛇的 Na_v 1.4 通道的结构域 IV 包含有 3 个氨基酸的置换,该地区束带蛇对 TTX 的耐受力比 Benton 地区的高两个数量级,因为后者只包含 1 个氨基酸替代[49, 63]。目前,只在河豚鱼与束带蛇中发现它们对河豚毒素的耐受性与其骨骼肌和神经元的钠离子通道发生了氨基酸替代有关。这两种生物之间的一个主要差别就是,几乎所有的河豚鱼对 TTX 都有一定的耐受性,而且有相同耐受机制,但是只有一部分束带蛇具有对 TTX 的耐受力。

5 河豚毒素研究展望

河豚毒素在海洋生物中的广泛分布,使其成为食用海产品中毒事件的一类重要致毒因子。由河豚毒素导致的中毒事件,主要是因为误食有毒河豚鱼,在中国、日本和东南亚的一些国家经常发生[65]。自 20 世纪 70 年代以来,我国沿海多次发生因食用织纹螺(*Nassarius* spp.)导致的中毒事件,导致数百人中毒甚至死亡。经分析发现,河豚毒素及其同系物是导致中毒的织纹螺体内主要的毒素成分[9, 66, 67]。织纹螺是一类腐食性生物,其体内的河豚毒素含量有明显的季节性变化特征,这可能与其在织纹螺中的生态作用有关。但是,对于织纹螺体内河豚毒素所具有的生态作用,毒素的可能来源、在织纹螺体内的代谢途径及生物合成机制等都不清楚,因此很难准确预测织纹螺的毒性变化,这在很大程度上限制了对食用织纹螺中毒事件的有效监测和管理。本文通过对河豚毒素及其同系物的种类组成、毒素在不同生物中的分布、在含毒生物中毒素可能具有的生态作用等进行综述,为河豚毒素的生态学研究提供了基础资料。同时,本文综述的结果也将为科学防范食用海产品中毒事件,以及河豚毒素解毒药品的研制提供思路。

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