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Yessotoxins: A toxicological overview

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ABSTRACT

Yessotoxins (YTXs) are polyciclic ether compounds produced by phytoplanktonic dinoflagellates and accumulated in filter feeding shellfish. These toxins can be ingested by humans through contaminated seafood consumption. Initially, YTXs were classified as Diarrhetic Shellfish (DS) toxins but the biological activity of these compounds, which lack of diarrheogenic effects, differs from that of diarrheic toxins. Thus, YTXs have been recently classified as a separate group of algal toxins.

Yessotoxin (YTX), homoyessotoxin and 45-hydroxy-homoyessotoxin are lethal after intraperitoneal injection to mice but not after single or repeated oral administration. The target organ seems to be the cardiac muscle cells, where these toxins induce light and electron microscopy ultrastructural changes not only after intraperitoneal injection, but also after oral exposure. On the other hand, di-desulfo-yessotoxin affects liver and pancreas, where it induces fatty degeneration. The mechanisms at the basis of the cardiac effects of YTX and homoyessotoxins are still not completely understood. No short term and chronic toxicity data are available as well as pharmacokinetic studies are lacking. Nevertheless, YTX is known to exert different *in vitro* activities, such as changes of intracellular calcium and cyclic AMP levels, alteration of cytoskeletal and adhesion molecules, caspases activation and opening of the permeability transition pore of mitochondria. This review reports the current knowledge on the *in vivo* toxicity and *in vitro* effects of these toxins.

1. Introduction

Yessotoxins (YTXs) are ladder-shaped polycyclic ether toxins, structurally related to brevetoxins and ciguatoxins (Ciminiello and Fattorusso, 2008). The parent compound of this class, yessotoxin (YTX; Fig. 1), has been initially isolated from the scallop *Patinopecten yessoensis* (Murata et al., 1987). Yessotoxin and its analogues are produced by the phytoplanktonic dinoflagellates *Protoceratium reticulatum* (=*Gonyaulax grindley*) (Satake et al., 1997), *Lingulodinium polyedrum* (=*Gonyaulax polyedra*) (Tubaro et al., 1998; Paz et al., 2004) and *Gonyaulax spinifera* (Rhodes et al., 2006). When environmental conditions promote the growth of these species, their toxins accumulate in edible tissues of filter feeding shellfish exposed to these dinoflagellates, thus entering in the food chain.

YTX and its analogues were initially included in the Diarrhetic Shellfish Poisoning (DSP) toxins group mainly because they were detected together with okadaic acid and other lipophilic toxins during the shellfish extraction procedure for Diarrhetic Shellfish toxins mouse bioassay (Tubaro and Hungerford, 2007). Recently, YTXs have been classified and regulated separately from the diarrheic toxins okadaic acid and derivatives (CEE, 2002), since they do not share the same mechanism of action,

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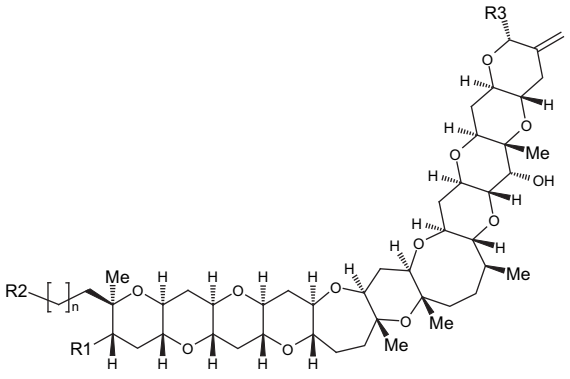


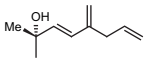
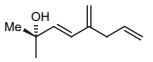
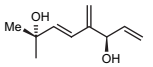
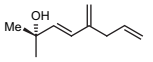
Toxin	R1	R2	R3	n
YTX	OSO_3H	OSO_3H		1
HomoYTX	OSO_3H	OSO_3H		2
45-OH-homoYTX	OSO_3H	OSO_3H		2
Di-desulfo-YTX	OH	OH		1

Fig. 1. Structures of YTX, homoYTX, 45-hydroxy-homoYTX and di-desulfo-YTX.

i.e. inhibition of protein phosphatases (Ogino et al., 1997).

More than 30 YTX analogues have been isolated so far from shellfish and microalgae (Paz et al., 2008). On the other hand, Miles et al. (2005a) revealed the presence of an array of more than 90 YTX analogues in one isolate of *Protoceratium reticulatum*, although structures for most of them have not been determined. Nevertheless, no human toxicity has been reported for YTXs, although YTXs contaminated-shellfish were worldwide recorded, sometimes at concentrations up to several mg/kg (Munday et al., 2008; Paz et al., 2008).

2. Pharmacokinetics/toxicokinetics

Information on absorption, distribution, metabolism and excretion of YTXs are still scanty, but toxicity data in mice suggest that they are poorly absorbed after oral intake. Tubaro et al. (2008a) demonstrated that YTX is at least partially absorbed at the gastrointestinal level after its administration for 7 days and quantified the toxin in the blood of mice. In particular, 24 h after the last daily oral administration (1 mg/kg/day), the toxin was detectable in the bloodstream by a direct enzyme linked immunosorbent assay (ELISA). A mean blood concentration of 3.12 ng YTX equivalents/ml of blood, corresponding to about 3 nM, was determined. However, considering the recovery rate of 54 % YTX from blood collection cards, a higher blood concentration of the toxin can be expected (about 6 ng/ml, corresponding to 5 nM).

3. *In vivo* effects of yessotoxin and its derivatives

3.1. Human toxicity

No reports of human poisoning induced by yessotoxins have been recorded, although YTXs contaminated shellfish are worldwide reported, sometimes at high concentrations (Munday et al., 2008; Paz et al., 2008).

3.2. In vivo *experimental toxicity*

Toxicological studies have been performed to define the LD_{50} (median lethal dose) values of YTX, di-desulfo-YTX, homoYTX and 45-hydroxy-homoYTX (Fig. 1) after acute and/or short-term treatment. For other YTX derivatives, literature data indicate that they induce lethality after intraperitoneal injection referred as "lethal dose", rather than LD_{50} value, possibly because they were obtained by a bioassay-oriented fractionation. Moreover, the experimental protocol, indicating the number of the used animals, strain, gender and administered doses, are often not presented. For two YTX derivatives, 1,3-enone isomer of heptenor-41-oxyessotoxin and the trihydroxylated amide of 9-methyl-41a-homoyessotoxin, literature data indicate that they do not induce lethality at 5 mg/kg after intraperitoneal injection (Miles et al., 2004, 2005b).

3.2.1. Acute intraperitoneal administration

YTX is lethal for mice after intraperitoneal (i.p.) injection, giving positive results at the official mouse bioassay for Diarrhetic Shellfish toxins detection (Terao et al., 1990; Ogino et al., 1997). Studies after acute intraperitoneal injection of YTX to mice revealed median lethal dose (LD_{50}) values in a wide range, from 80–100 to 750 μg/kg (Table 1) (Terao et al., 1990; Ogino et al., 1997; Aune et al., 2002, 2008, Tubaro et al., 2003). These differences can be attributed not only to different experimental conditions between laboratories, but also to the use of mice of different age, strain and gender (Aune et al., 2008).

Among YTX derivatives, only homoYTX, 45-hydroxy-homoYTX and di-desulfo-YTX were evaluated for their toxicity after intraperitoneal injection to mice. LD_{50} value of homoYTX was 444 μg/kg, being in the range of LD_{50} values recorded for YTX, and di-desulfo-YTX was lethal for mice at 301 μg/kg; 45-hydroxy-homoYTX was shown to be less toxic than YTX as it did not induce mice lethality or symptoms of toxicity at 750 μg/kg (Table 1) (Terao et al., 1990; Tubaro et al., 2003). The toxicity of other analogues was quoted as lethal dose after i.p. injection to mice: a value of about 220 μg/kg was reported for 45,46,47-trinorYTX, whereas more than two fold high value (about 500 μg/kg) was recorded for 45-hydroxy-YTX, carboxy-YTX, carboxy-homoYTX and 1-desulfo-YTX (Table 1) (Satake et al., 1996; Daiguji et al., 1998; Ciminiello et al., 2000a,b). In addition, adriatoxin seems to posses a lethal effect slightly lower than that of YTX but no further details were reported by the authors (Ciminiello et al., 1998).

After intraperitoneal injection of lethal doses of YTX or homoYTX, restlessness, dyspnoea, shivering, jumping and/or cramps were recorded in mice (Aune et al., 2002; Tubaro et al., 2003). Necroscopic examination of mice treated with