Environmental Toxicology and Pharmacology 48 (2016) 7–16

Contents lists available at ScienceDirect

Environmental Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/etap

Review or Mini-review

Low dose extended exposure to saxitoxin and its potential neurodevelopmental effects: A review

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ARTICLE INFO

Article history:
Received 8 September 2016
Accepted 27 September 2016
Available online 28 September 2016

Keywords:
Saxitoxin
Voltage gated sodium channel
Neurodevelopment
Drinking water
Seafood

ABSTRACT

Saxitoxin (STX) and its analogs, the paralytic shellfish toxins (PSTs), are a group of potent neurotoxins well known for their role in acute paralytic poisoning by preventing the generation of action potentials in neuronal cells. They are found in both marine and freshwater environments globally and although acute exposure from the former has previously received more attention, low dose extended exposure from both sources is possible and to date has not been investigated. Given the known role of cellular electrical activity in neurodevelopment this pattern of exposure may be a significant public health concern. Additionally, the presence of PSTs is likely to be an ongoing and possibly increasing problem in the future. This review examines the neurodevelopmental toxicity of STX, the risk of extended or repeated exposure to doses with neurodevelopmental effects, the potential implications of this exposure and briefly, the steps taken and difficulties faced in preventing exposure.

Contents

Abbriviations: STX, Saxitoxin; PST, Paralytic Shellfish Toxin; PSP, paralytic shellfish poisoning; VGSC, voltage-gated-sodium channel; GTX, Gonyautoxins; EFSA, European Food Safety Authority; hERG, human ether-a-go-go; TTX, Tetrodotoxin; LPS, lipopolysacharride; SOD, superoxide dismutase; GPx, glutathione peroxidase; EROD, ethoxyresorufin-0-deethylase; PROD, penthoxyresorufin-0-deethylase; PAC, powdered activated carbon.

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http://dx.doi.org/10.1016/j.etap.2016.09.020
1382-6689/

1. Introduction

STX is a neurotoxin most commonly known for its role in paralytic shellfish poisoning (PSP) and the majority of past research has been focused on acute exposure from this source. However, there is also the potential of extended exposure to low doses of the toxin, from this source and others, and this pattern of exposure has not been thoroughly investigated. While exposure to high doses of STX can be fatal, low dose extended exposure has the potential to affect neurodevelopment through the action of the toxin at voltage-gated sodium channels (VGSCs) which have been shown to play an important role in a developing nervous system.

Low dose extended exposure from shellfish may occur in communities which rely heavily on a seafood diet, consuming more than the daily average and for considerable periods of time. Additionally at risk are small isolated coastal communities who may harvest untested shellfish. It has been shown that tolerance can occur in some populations (Kuiper-Goodman et al., 1999) so that communities harvesting untested shellfish may be exposed to concentrations higher than safety guidelines, which would cause acute poisoning in a sensitive individual, but would go unnoticed in a tolerant individual. In such cases, while acute poisonings may not occur more subtle low dose adverse effects may be taking place.

The toxin is also produced at lower concentrations by freshwater cyanobacteria which can be found in fresh water sources from which drinking water is sourced (Hoeger et al., 2004). Based on human data from acute paralytic shellfish poisoning events, a drinking water guideline value of 3 μg/L has been established in multiple countries including Australia, Brazil and New Zealand (Burch, 2008; ADWG, 2011) and there have been no acute poisonings to date (Zegura et al., 2011).

There are multiple water treatment methods available for the removal of the cyanobacterial cells responsible for the production of STX and the extracellular dissolved toxin (Hoeger et al., 2004). The percentage of each removed depends on the methods used and while consumers are protected from acute toxicity, low dose exposure can still occur and could occur for extended periods of time considering the duration of algal blooms. Although extended low dose extended exposure is more likely via drinking water there is no guideline for long-term exposure as there has been no research into this pattern of exposure.

It has been suggested that the predicted future climatic changes of global warming such as increased water temperatures, nutrient loading and stratification as well as altered hydrology will favor freshwater cyanobacterial growth and give cyanobacteria a competitive advantage over other phytoplankton. In fact harmful algal blooms in marine settings have already been seen to increase since the 1970s (Hallegraeff, 1993; Van Dolah, 2000) and an increase in total cyanobacteria numbers and individual algal bloom durations has been noted since the 1980s (Croome et al., 2011). Additionally the link between algal blooms and eutrophication has been noted since the 1980s (Anderson et al., 2002).

2. STX and its analogs

STX itself is part of a large group of analogs collectively known as the paralytic shellfish toxins (PSTs) or in some cases the saxitoxins. This group has a long history with human poisonings dating back to at least 1793 (Price et al., 1991). Despite this history the toxin was not isolated until 1957 from the butter clam *Saxidomus giganteus*, after which the toxin is named (Schantz et al., 1957). Due to its noncrystalline and highly polar nature, the structure of the toxin was not determined for almost another 20 years (Schantz et al., 1975). STX is one of the most potent natural toxins known, with a place on Schedule 1 of the Chemical Weapons Convention (Llewellyn, 2006b).

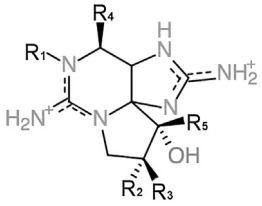

Fig. 1. The tetrahydropurine skeleton of STX and its analogs, for R group substituents see Table 1.

The PST analogs all share a 3,4,6-trialkyl tetrahydropurine skeleton with two guanidinium groups (Schantz et al., 1975) (Fig. 1). Variations to the side chains give the analogs varying levels of toxicity and the analogs are grouped depending on their side chain variations. STX and neoSTX are non-sulfated, the Gonyautoxins (GTXs) mono-sulfated and the C-toxins di-sulfated, each respectively less toxic than STX. Further variants include decarbamoyls. Authors have described up to 57 analogs (Wiese et al., 2010), with the most common shown in Table 1. STX is highly polar and stable in solution (Schantz et al., 1957) while the c-toxins and GTXs are not particularly stable and can degrade to produce more toxic analogs (Fanger et al., 1995). So while the concentration of individual analogs will vary the group of toxins can persist in water for long periods of time, therefore there is a potential for extended exposure periods.

2.1. Sources of STX exposure

As mentioned, STX and its analogs are produced in both marine and freshwater environments. It was originally thought that both marine dinoflagellates and freshwater cyanobacteria produce PSTs by the same biosynthetic pathway (Shimizu, 1993), which is mediated by the *stx* gene cluster in cyanobacteria (Kellmann et al., 2008; Mihali et al., 2009) but the genes responsible for toxin production in dinoflagellates are now thought to be quite different (Yang et al., 2010). It has been recently shown that only a small number of the proteins involved in the biosynthetic pathway in cyanobacteria are present in dinoflagellates, so that the later steps in the pathway may be performed by different reactions or enzymes (Hackett et al., 2013).

The reason why either of these organisms produce the toxin is unknown although there are theories, the most common being defense but from what is not known. Another theory suggests a relationship between intracellular Na^+ levels and STX production, where toxic strains of cyanobacteria would be at an advantage under conditions of high pH or Na^+ stress (Pomati et al., 2004a,b). Based on genetic analysis it has been suggested that the *stx* gene cluster could have emerged at least 2100 Ma, in an environment significantly different to today. At that time organisms had not evolved VGSCs, the most well known target of the PSTs, and so another theory is that the evolutionary predecessor of the channel, the potassium channels, could have been the target of the toxin (Murray et al., 2011).

2.1.1. Marine production of STX

The most well-known and researched source of the STXs are the marine dinoflagellates from the genera *Alexandrium, Gymnodinium* and *Pyrodinium* (Harada et al., 1982; Lefebvre et al., 2008; Oshima et al., 1987). The marine dinoflagellates produce PSTs which are consumed by invertebrates such as shellfish, crustaceans and molluscs, and rarely fish (Deeds et al., 2008). The majority of