# Chapter 16: Toxin types, toxicokinetics and toxicodynamics

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## Introduction

Cyanobacteria produce a wide array of bioactive secondary metabolites (see Table A.1 in Appendix A), some which are toxic (Namikoshi and Rinehart 1996; Skulberg 2000). Those toxic to mammals include the microcystins, cylindrospermopsins, saxitoxins, nodularins, anatoxin-a, homoanatoxin-a, and anatoxin-a(s). It has been recently suggested that β-methylamino alanine (BMAA) may be a new cyanobacterial toxin (Cox et al. 2003; Cox et al. 2005). The public health risks of cyanotoxins in drinking water have recently been reviewed (Falconer and Humpage 2005b). The aim of this paper is to concisely review our current knowledge of their acute toxicity, mechanisms of action, toxicokinetics and toxicodynamics.

## Microcystins

Microcystins (MCs) are a group of at least 80 variants based on a cyclic heptapeptide structure (Fig. 1). All toxic microcystin structural variants contain a unique hydrophobic amino acid, 3-amino-9-methoxy-10-phenyl-2,6,8-trimethyl-deca-4(E),6(E)-dienoic acid (ADDA). The prototype-compound is MC-LR, which has leucine and arginine at the two hypervariable positions in the ring structure (X and Y, respectively, in Fig. 1). Sub-

stitution of other amino acids at these sites, or methylation of residues at other sites, leads to wide structural variability (Namikoshi et al. 1990; Namikoshi et al. 1992d; Namikoshi et al. 1992b; Namikoshi et al. 1992c; Namikoshi et al. 1992a; Namikoshi et al. 1995; Namikoshi et al. 1998; Sivonen and Jones 1999). These toxins are produced by a wide variety of planktonic cyanobacteria including *Microcystis aeruginosa, M. viridis, M. ichthyoblabe, M. botrys, Planktothrix argardhii, P. rubescens, P. mougeotii, Anabaena flos-aquae, A. circinalis, A. lemmermannii, Nostoc spp.,* and *Snowella lacustris* (Botes et al. 1982; Codd and Carmichael 1982; Botes et al. 1985; Kusumi et al. 1987; Krishnamurthy et al. 1989; Sivonen et al. 1990; Harada et al. 1991; Watanabe et al. 1991; Sivonen et al. 1992; Ueno et al. 1996; Vezie et al. 1998; Marsalek et al. 2000; Fastner et al. 2001). The species most often cited as microcystin producers are *M. aeruginosa* (worldwide) and the *Planktothrix* species (Northern Europe). Microcystin production has also been linked with some benthic species: *Haphalosiphon hibernicus* and *Oscillatoria limnosa* (Prinsep et al. 1992b; Mez et al. 1997). Other benthic species have been implicated, but the difficulty of culturing these species has precluded clear identification of the organisms responsible.

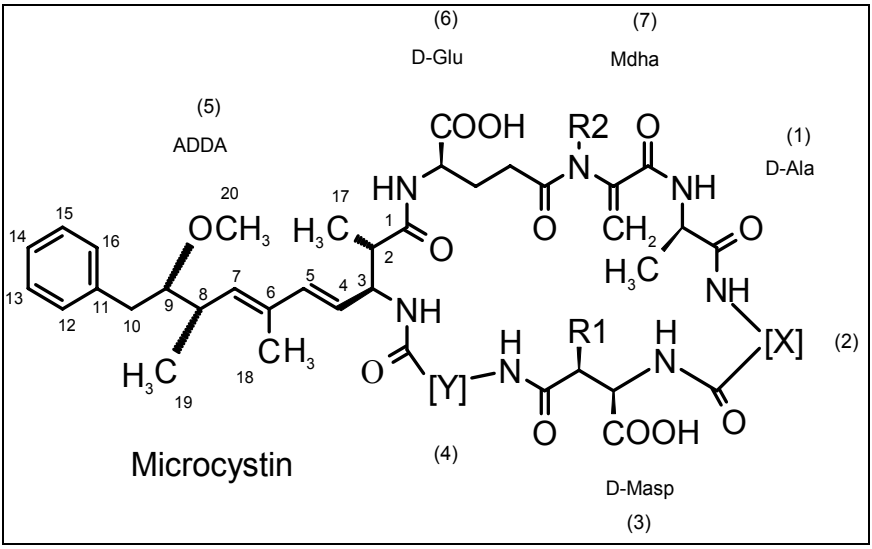


**Fig. 1.** General structure of the microcystins

The primary site of toxic action of the microcystins is the active site of protein phosphatases 1 and 2A (Eriksson et al. 1990; MacKintosh et al. 1990; Runnegar et al. 1995b). This activity is mediated principally by the

ADDA group (Goldberg et al. 1995) although most microcystin variants contain dehydroalanine, which can undergo covalent linkage to a cysteinyl sulphur on the phosphatase. This makes the inhibition irreversible.

MC-LR has a $LD_{50}$ (ip, mice, 24hr) of 60 μg $kg^{-1}$. The primary acute effect of protein phosphatase inhibition is hyperphosphorylation of many cellular proteins including the hepatocellular cytoskeleton, which causes loss of cell-cell contacts and intra-hepatic haemorrhage. Death is due to hypovolemic shock (Runnegar and Falconer 1986; Falconer and Yeung 1992; Runnegar et al. 1993). Other acute effects include altered mitochondrial membrane permeability, generation of reactive oxygen species and induction of apoptosis (Fladmark et al. 1999; Humpage and Falconer 1999; Ding et al. 2000; Hooser 2000), most likely due to a fatal loss of control of regulatory phosphorylation. Uptake is via specific organic anion transport proteins (Runnegar et al. 1991; Runnegar et al. 1995a; Fischer et al. 2005); hence MCs exhibit a predominantly hepatic organotropism, although enteric and even dermal effects have been demonstrated in certain circumstances (Falconer and Buckley 1989; Falconer et al. 1992). Studies of tissue distribution using radio-labelled toxin have confirmed the liver as the main site of toxin accumulation (~70% of a sub-lethal iv dose) and that the toxin level in this organ remains constant for up to 6 days post treatment (Falconer et al. 1986; Runnegar et al. 1986; Brooks and Codd 1987; Robinson et al. 1989; Robinson et al. 1990; Robinson et al. 1991). Bile acids and compounds that block bile acid uptake inhibit microcystin hepatic uptake and toxicity (Runnegar et al. 1981; Thompson et al. 1988; Thompson and Pace 1992; Runnegar et al. 1995a). Formation of glutathione metabolites of MC-LR and MC-RR has been demonstrated (Kondo et al. 1996). Toxin is rapidly cleared from the blood, after which time the main albeit slow route of excretion is via the faeces (Robinson et al. 1991). Human acute intoxication via renal dialysis (possibly in combination with cylindrospermopsin) resulted in visual disturbances, nausea, vomiting and death from liver failure (Carmichael et al. 2001; Azevedo et al. 2002), whereas sub-lethal exposure resulted in elevation of liver enzyme activities in the serum (Falconer et al. 1983).

Lower microcystin concentrations (pM) appear to suppress apoptosis and promote cell division in polyploid hepatocytes in vitro (Humpage and Falconer 1999), effects which may be linked to the enhancement of the growth of hepatic and colonic pre-cancerous lesions in animal models (Fujiki and Suganuma 1993; Ito et al. 1997; Humpage et al. 2000b). Microcystin exposure has been linked to human liver and colon cancer incidence (Yu 1995; Fleming et al. 2002; Zhou et al. 2002).

## Cylindrospermopsins

The cylindrospermopsins (CYNs, Fig. 2) are alkaloids comprised of a tricyclic guanidino moiety linked via a hydroxylated bridging carbon (C7) to uracil (Ohtani et al. 1992). Structural variants are 7-epi-CYN and 7-deoxy-CYN (Norris et al. 1999; Banker et al. 2000), the latter having slightly lower potency than the 7-hydroxylated variants (Looper et al. 2005). The uracil moiety is required for toxicity (Banker et al. 2001; Runnegar et al. 2002). CYN's are produced by *Cylindrospermopsis raciborskii, Aphanizomenon ovalisporum, Anabaena bergii, Umezakia natans, Raphidiopsis curvata*, and as yet other unidentified species (Hawkins et al. 1985; Harada et al. 1994; Banker et al. 1997; Hawkins et al. 1997; Shaw et al. 1999; Li et al. 2001a; Schembri et al. 2001).

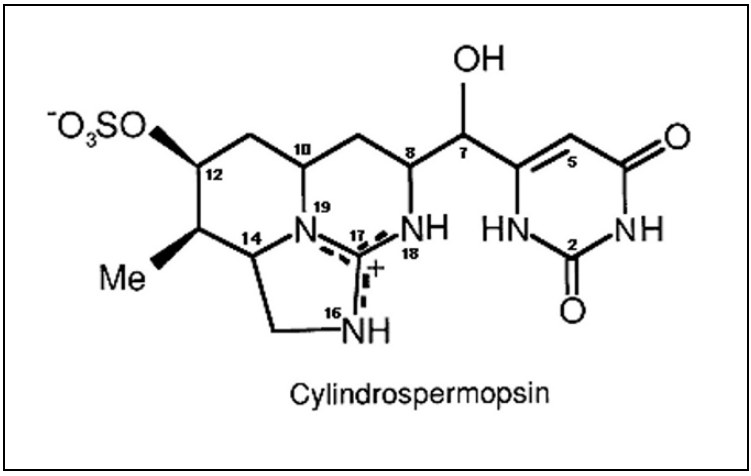


**Fig. 2.** Structure of cylindrospermopsin

The $LD_{50}$ of CYN indicates a delayed toxicity (2.0 mg $kg^{-1}$, ip mouse, after 24 hrs but 0.2 mg $kg^{-1}$ after 5 days; Ohtani et al. 1992). The primary toxic effect of the parent compound appears to be irreversible protein synthesis inhibition (Terao et al. 1994; Froscio et al. 2001, 2003; Looper et al. 2005). However, there is also evidence for metabolic activation as inhibitors of CYP450's are able to reduce acute toxicity (Runnegar et al. 1994; Froscio et al. 2003), CYN-dependent inhibition of glutathione synthesis (Runnegar et al. 1995c), and genotoxicity (Humpage et al. 2005). The evidence for CYP450 involvement in the in vivo toxicosis is less clear (Norris et al. 2002). Acute CYN poisoning results in lipid accumulation in the liver followed by hepatocellular necrosis (Terao et al. 1994; Seawright et al.

1999). Non-hepatic effects include destruction of the proximal tubules of the kidney (Falconer et al. 1999), as well as cytotoxic and thrombotic effects in other tissues. Intraperitoneal injection of radio-labelled CYN resulted in predominantly hepatic and, to a lesser extent, renal distribution of the toxin (Norris et al. 2001). There was some evidence for the formation of metabolites, but these were not characterised. Sub-chronic oral exposure resulted in mainly hepatic and renal effects (Humpage and Falconer 2003). Effects of poisoning in humans included hepatoenteritis and renal insufficiency (Byth 1980).

Genotoxic effects of CYN have been demonstrated in vitro using the cytokinesis-blocked micronucleus assay (Humpage et al. 2000a) and the comet assay (Humpage et al. 2005). Strand breakage and loss of whole chromosomes were demonstrated to occur at concentrations below those that caused overt cytotoxicity. Hepatic DNA fragmentation has also been demonstrated in vivo after a single intraperitoneal dose of cylindrospermopsin (Shen et al. 2002). There is some evidence of carcinogenicity in vivo (Falconer and Humpage 2001), but more work is required to confirm this.

## Saxitoxins (Paralytic Shellfish Toxins (PSTs))

The saxitoxins (Fig. 3) have been extensively studied due to their involvement in paralytic shellfish poisoning where toxigenic marine dinoflagellates are consumed by shellfish, which concentrate the toxins and can deliver toxic quantities to consumers of the shellfish (Kao 1993). Saxitoxins are alkaloids based on a 3,4,6-trialkyl tetrahydropurine skeleton which can be further carbamylated, sulphated or N-sulphocarbamylated to produce a range of perhaps 30 analogues (Shimizu 2000), some of which are found only in freshwater cyanobacteria (Onodera et al. 1997b; Lagos et al. 1999; Molica et al. 2002). They are produced in the freshwater environment by *Aphanizomenon* spp.*, Anabaena circinalis, Cylindrospermopsis raciborskii, Lyngbya wollei, Planktothrix* spp., and other unidentified species (Jackim and Gentile 1968; Ikawa et al. 1982; Humpage et al. 1994; Carmichael et al. 1997; Lagos et al. 1999; Kaas and Henriksen 2000; Pomati et al. 2000; Li et al. 2000; Li et al. 2003).

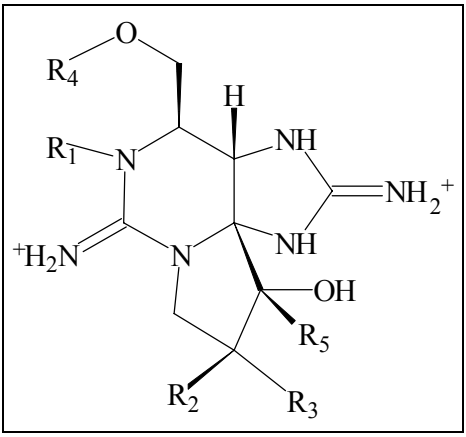


**Fig. 3.** General structure of the saxitoxins

| Toxin | R1 | R2 | R3 | R5 | Net Charge | Relative mouse toxicity |
|---|---|---|---|---|---|---|
| *R4 = $CONH_2$ (carbamate toxins)* | | | | | | |
| STX | H | H | H | OH | +2 | 1.000 |
| neoSTX | OH | H | H | OH | +2 | 0.924 |
| GTX1 | OH | H | $OSO_3^-$ | OH | +1 | 0.994 |
| GTX2 | H | H | $OSO_3^-$ | OH | +1 | 0.359 |
| GTX3 | H | $OSO_3^-$ | H | OH | +1 | 0.638 |
| GTX4 | OH | $OSO_3^-$ | H | OH | +1 | 0.726 |
| *R4 = $CONHSO_3^-$ (n-sulfocarbamoyl (sulfamate) toxins)* | | | | | | |
| GTX5 (B1) | H | H | H | OH | +1 | 0.064 |
| GTX6 (B2) | OH | H | H | OH | +1 | - |
| C1 | H | H | $OSO_3^-$ | OH | 0 | 0.006 |
| C2 | H | $OSO_3^-$ | H | OH | 0 | 0.096 |
| C3 | OH | H | $OSO_3^-$ | OH | 0 | 0.013 |
| C4 | OH | $OSO_3^-$ | H | OH | 0 | 0.058 |
| *R4 = H (decarbamoyl toxins)* | | | | | | |
| dcSTX | H | H | H | OH | +2 | 0.513 |
| dcneoSTX | OH | H | H | OH | +2 | - |
| dcGTX1 | OH | H | $OSO_3^-$ | OH | +1 | - |
| dcGTX2 | H | H | $OSO_3^-$ | OH | +1 | 0.651 |
| dcGTX3 | H | $OSO_3^-$ | H | OH | +1 | 0.754 |
| dcGTX4 | OH | $OSO_3^-$ | H | OH | +1 | - |
| LWTX4 | H | H | H | H | +2 | <0.004 |

| | | | | | | |
|---|---|---|---|---|---|---|
| *R4 = $COCH_3$ (Lyngbya wollei toxins)* | | | | | | |
| LWTX1 | H | $OSO_3^-$ | H | H | +1 | <0.004 |
| LWTX2 | H | $OSO_3^-$ | H | OH | +1 | 0.072 |
| LWTX3 | H | H | $OSO_3^-$ | OH | +1 | 0.021 |
| LWTX5 | H | H | H | OH | +2 | 0.139 |
| LWTX6 | H | H | H | H | +2 | <0.004 |
| *R4 = $COC_6H_4OH$ (Gymnodinium catenatum toxins)* | | | | | | |
| GC1 | H | H | $OSO_3^-$ | OH | +1 | - |
| GC2 | H | $OSO_3^-$ | H | OH | +1 | - |
| GC3 | H | H | H | OH | +2 | - |

Modified from Nicholson and Burch (2001)

**Fig. 3 (cont).** General structure of the saxitoxins

These toxins are potent voltage-gated sodium channel antagonists, causing numbness, paralysis and death by respiratory arrest. Analogue potency varies greatly, with saxitoxin having an $LD_{50}$ (ip mouse) of 10 μg $kg^{-1}$, but C1 being at least 160-fold less toxic (Oshima 1995). Toxin uptake and toxicokinetics of a number of analogues have been studied in cats (Andrinolo et al. 1999; Andrinolo et al. 2002b; Andrinolo et al. 2002a). Oral uptake was efficient, and toxin distributed rapidly throughout the body, including the brain. Clearance was via simple glomerular filtration, and there was no evidence of metabolism of the toxins. Toxicological studies to date have assumed the acute exposure paradigm of shellfish poisoning rather than sub-chronic low-dose as might be expected from drinking water. Evidence for development of tolerance to PSTs has been presented (Kuiper-Goodman et al. 1999). Neuro-developmental disturbances have been demonstrated in fish (Lefebvre 2002) but these have not been studied in mammals.

## Nodularins

Nodularins (Fig. 4) are hepatotoxic cyclic peptides of similar structure to the microcystins except that they are composed of 5 amino acids rather than 7 (Rinehart and Namikoshi 1994). Variants due to substitution of arginine with homoarginine or valine (motuporin) have been described (de Silva et al. 1992; Namikoshi et al. 1993; Namikoshi et al. 1994), but these appear to be relatively rare. ADDA is still present but dehydroalanine is replaced by N-methyl-dehydrobutyrine (Rinehart et al. 1988). The smaller

ring size prevents this latter moiety from coordinating with the phosphatase cysteine, and so nodularin does not bind covalently (Lanaras et al. 1991; Craig et al. 1996; Bagu et al. 1997). However, due to the high affinity of ADDA for the active site, this lack of covalent binding does not affect toxin potency, which is similar to that of microcystin-LR (Ki's are of the order 0.1 – 1.5 nM; Honkanen et al. 1990; MacKintosh et al. 1990; Honkanen et al. 1991). This lack of covalent binding may allow nodularin to reach other sites in the cell, and this has been suggested as a mechanism by which this toxin might act as a direct carcinogen (Ohta et al. 1994; Bagu et al. 1997). *Nodularia spumigena* appears to be the sole freshwater cyanobacterial source of nodularin (motuporin was isolated from a marine sponge). *N. spumigena* generally prefers brackish waters and so has had only localised impacts on human drinking water sources (for example, in Lake Alexandrina, South Australia in the early 1990's).

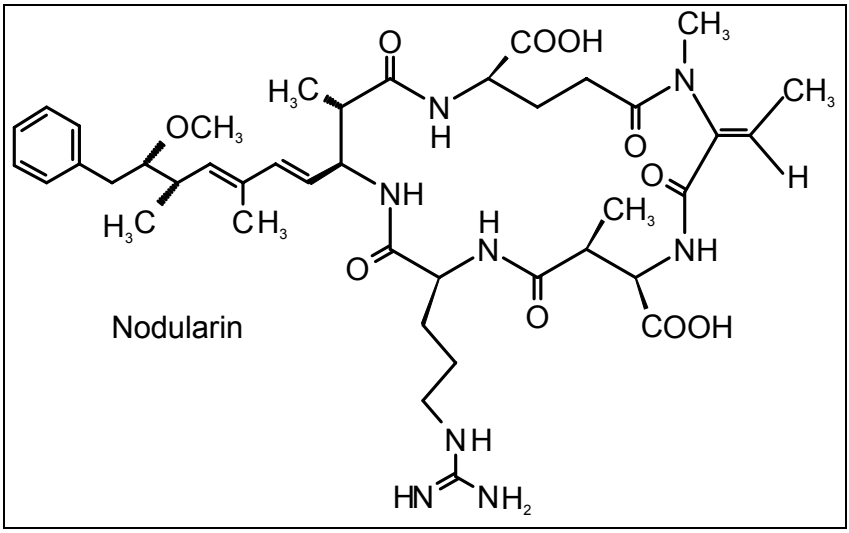


**Fig. 4.** Structure of nodularin

## Anatoxin-a/Homoanatoxin-a

Anatoxin-a (2-acetyl-9-azabicyclo(4-2-1)non-2-ene; (Fig. 5) and/or homoanatoxin-a (propionyl residue replaces acetyl at C2) are produced by *Anabaena flos-aquae, A. planktonica, Aphanizomenon spp., Planktothrix formosa*, and a benthic *Oscillatoria* spp. (Carmichael et al. 1975; Carmichael and Gorham 1978; Sivonen et al. 1989; Edwards et al. 1992; Skulberg et al. 1992; Bruno et al. 1994; Bumke-Vogt et al. 1999). These toxins are

nicotinic acetylcholine receptor agonists having a $LD_{50}$ of 200 μg $kg^{-1}$ (Carmichael et al. 1979; Carmichael 1994). Residence of these toxins at post-synaptic cholinergic receptors results in nerve depolarisation (Swanson et al. 1990; Huby et al. 1991; Swanson et al. 1991; Wonnacott et al. 1991). Typical symptoms in mice are loss of muscle coordination, gasping, convulsions and death within minutes from respiratory arrest (Carmichael et al. 1979). Dog deaths have been attributed to poisoning by these toxins when the animals have licked their coats after swimming (Codd et al. 1992; Edwards et al. 1992; Falconer and Nicholson, personal communication). A single human fatality has been attributed to poisoning by anatoxin-a after the victim swam in a scum-covered pond (Behm 2003), but further investigation suggests that this is unlikely to be correct (Carmichael et al. 2004). Anatoxins have not been linked to human poisoning via drinking water, although evidence has been presented that such a risk may exist in Florida (Burns 2005).

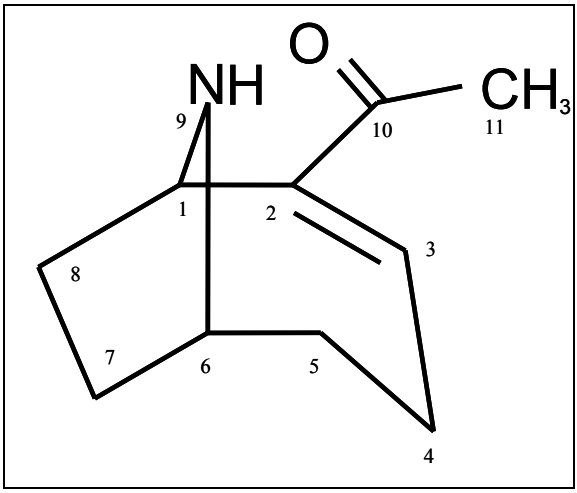


**Fig. 5.** Structure of anatoxin-a

## Anatoxin-a(s)

Anatoxin-a(s) (Fig. 6) is a phosphorylated cyclic N-hydroxyguanine, with a structure and action similar to organophosphate pesticides (Mahmood and Carmichael 1986, 1987; Hyde and Carmichael 1991). It is a potent acetylcholinesterase inhibitor with a $LD_{50}$ (ip, mouse) of 20 μg $kg^{-1}$. The in vivo toxic effects are similar to those of anatoxin-a but with the addition of salivation (hence the "s") and lacrimation (Mahmood and Carmichael

1986, 1987; Matsunaga et al. 1989). Anatoxin-a(s) is produced by *Anabaena flos-aquae* and *A. lemmermannii* (Matsunaga et al. 1989; Onodera et al. 1997a), and the latter has been implicated in the deaths of water birds in Denmark (Onodera et al. 1997a). No human illness has been attributed to this toxin.

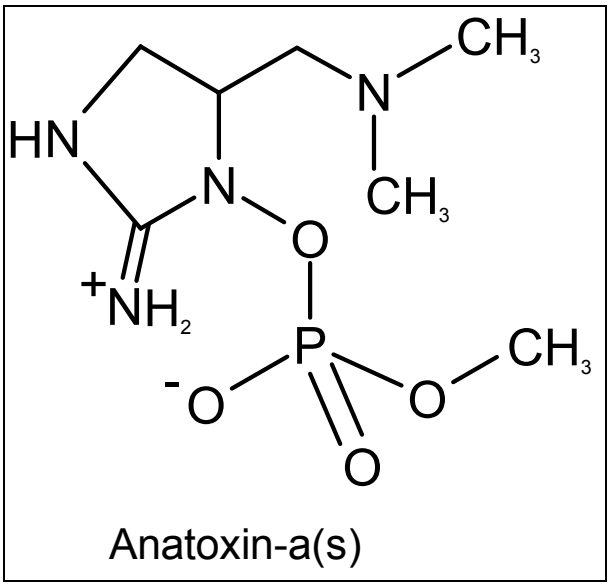


**Fig. 6.** Structure of anatoxin-a(s)

## β-Methylamino alanine

β-Methylamino alanine (BMAA) (Fig. 7) is an old toxin that has recently been found to be of cyanobacterial origin (Cox et al. 2005). Whether cyanobacteria are the only source is not known. BMAA was described in 1967 in extracts of cycad seeds from Guam, and suggested as a possible causative agent of certain neurodegenerative disorders that were prevalent on the island (Vega and Bell 1967). Early studies in monkeys dosed with high levels of BMAA produced effects similar to those seen in humans (Spencer et al. 1987). BMAA was found to be a glutaminergic agonist capable of producing excitotoxicity, but only at relatively high concentrations ($EC_{50}$ in cell-lines of 300 μM; Weiss et al. 1989a; Weiss et al.

1989b). Sodium bicarbonate is required as a cofactor due to the spontaneous formation of the carbamate, turning the monocarboxylic BMAA into a dicarboxylic glutamate mimic (Myers and Nelson 1990). Toxicokinetic studies in rats and monkeys demonstrated rapid and virtually complete uptake via the oral route, and distribution throughout the body, including the brain (Duncan et al. 1991; Duncan et al. 1992), although the latter organ only contained about 0.08% of the administered dose by 48 hrs. There was evidence of active transport across the blood-brain barrier via the large neutral amino acid carrier (Km=2.9mM), but this would not be rapid when BMAA is in competition with normal levels of natural amino acids (Duncan et al. 1992; Jalaludin and Smith 1992). Approximately 1.4% of an oral dose, and 1.8% of an iv dose, were excreted unmetabolised in the urine by 48 hrs, whereas approximately 22% could be accounted for in total (unmetabolised plus acid hydrolysable; Duncan et al. 1992; Jalaludin and Smith 1992). L-amino acid oxidase has been shown to metabolise BMAA, eventually leading to N-methylglycine, but the rate appears to be quite slow (Hashmi and Anders 1991). Multiple sub-lethal doses were shown to be non-cumulative (Seawright et al. 1990). Based on these and other studies, and the likely concentrations of BMAA in cycad seed flour, it was suggested that this toxin was unlikely to be the sole causative agent of the Guam neurodegenerative disease (Duncan et al. 1990). The hypothesis that BMAA might bio-accumulate in cycad seed-consuming flying foxes (Cox and Sacks 2002), and then the demonstration of high levels of the toxin not only in museum exhibits of flying foxes, but also in the brains of patients who died from neurodegenerative disorders in both Guam and Canada, has re-ignited the debate (Banack and Cox 2003; Cox et al. 2003; Murch et al. 2004a; Murch et al. 2004b). Finally, the demonstration that many species of cyanobacteria produce BMAA (Cox et al. 2005) has made this an issue of potential concern for the provision of safe drinking water. Much more work needs to be done before a proper assessment can be made of this "new" cyanotoxin.

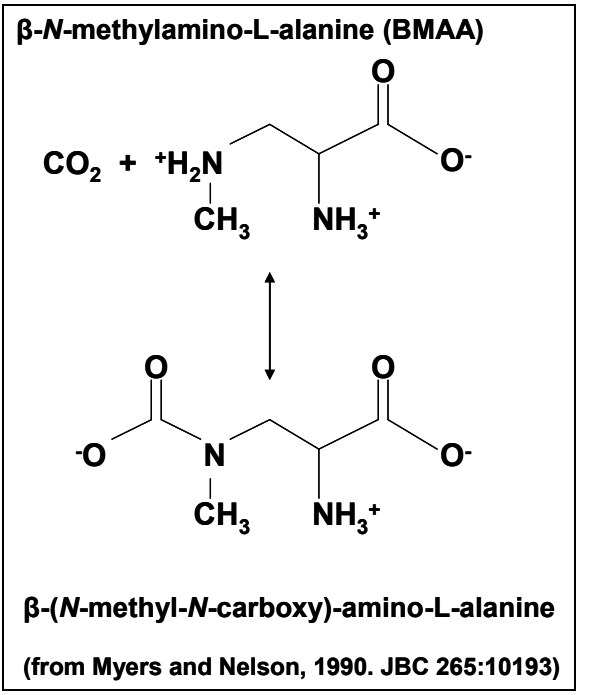


**Fig. 7.** Structure of BMAA and its reaction with $CO_2$.

## Undiscovered cyanotoxins and other cyanobacterial bioactive compounds

Given the range of bioactive compounds known to be produced by cyanobacteria (see Table A.1 in Appendix A for a non-exhaustive list of "non-cyanotoxin" cyanobacterial bioactive compounds) it is not surprising that a few have turned out to be toxic to mammals. It is unlikely that we have found all of the toxins because unexplained toxicity has been observed, for example, in *C. raciborskii* (Hawkins et al. 1997; Bernard et al. 2003; Fastner et al. 2003; Saker et al. 2003), in *Anabaena* spp. (Baker and Humpage 1994), and in a *Phormidium* spp. (Baker et al. 2001). Furthermore, new toxin analogues continue to be reported (Onodera et al. 1997b; Banker et al. 2000; Molica et al. 2002; Negri et al. 2003). The fact that known toxins are usually found in new locations once people look for them, for example, recent discoveries of CYN in New Zealand (Stirling and Quilliam 2001), Thailand (Li et al. 2001b), Germany (Fastner et al. 2003), Brazil (Carmichael et al. 2001) and Florida (Burns 2005), suggests that the toxigenic species are widespread and that no country should consider itself immune

from the risk to public health even from the known toxins. A further point that needs reinforcing is that single microcystins or single cylindrospermopsins almost never occur in nature. Instead mixtures of toxins are the norm, and so we need to understand toxin interactions. This will enable the calibration of studies done using MC-LR and the formulation of regulations to be based on toxicity equivalents rather than quantities of individual compounds.

## Research Needs

Research into the toxicology of cyanotoxins is still lacking in a number of important areas:

- Microcystins:
  - Epidemiological studies into links with human cancer. This requires a biomarker of low dose exposure for which ELISA may be an option (Hilborn et al. 2005).
  - Chronic animal studies into links with cancer.
  - Effects of mixtures of microcystin analogues, and of microcystins with cylindrospermopsin.
- Cylindrospermopsin:
  - Human effects – An opportunity exists for follow-up of exposed humans on Palm Island, Australia.
  - Animal studies for Guideline formulation: Toxicokinetics, Chronic exposure, Carcinogenicity, Reproductive toxicity.
  - Effects of mixtures (with microcystins).
  - Cell-based studies: To better understand mechanism(s) of toxic and genotoxic action, leading to identification of biomarkers of exposure & effect (Falconer and Humpage 2005a).
- Neurotoxins:
  - Episodic and chronic low dose exposures – particularly any effect on neural development.
- BMAA:
  - Confirm association with neurodegenerative disease.
  - Mechanism of bioaccumulation.
  - Mechanism of toxicity (glutaminergic excitotoxicity or other effects eg disruption of protein structure/function?).
  - Trophic studies to determine routes of human exposure.

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## Appendix A

**Table A.1.** Some of the many bioactive compounds that have been isolated from cyanobacteria

| Name | Chemical Class | Activity | Source | Reference |
|---|---|---|---|---|
| Acutiphycin | - | Antineoplastic | Oscillatoria acutissima | (Barchi et al. 1984) |
| Aeruginosins | Linear depsipeptides | Protease inhibitors | Microcystis spp., Oscillatoria spp. | (Murakami et al. 1994) |
| Aeruginoguanidines | Peptide | Cytotoxic | M. aeruginosa | (Ishida et al. 2002) |
| Anabaenapeptins | Cyclic peptides | Vasodilation | Anabaena flos-aquae, other spp. | (Harada et al. 1995) |
| Antillatoxin | Cyclic lipopeptide | Ichthyotoxin | Lyngbya majuscula | (Orjala et al. 1995) |
| Aphanorphine | Alkaloid | - | Aphanizomenon flos-aquae | (Gulavita et al. 1988) |
| Aplysiatoxins | Phenolic bislactone | Tumour promoters | Lyngbya majuscula | (Fujiki et al. 1985; Fujiki and Sugimura 1987) |
| Apoptogens | Unknown | Induction of apoptosis | Various benthic species | (Herfindal et al. 2005) |
| "Bioactive compounds" | - | - | Nostoc muscorum | (De Mule et al. 1991) |
| Calophycin | Decapeptide | Antifungal | Calothrix fusca | (Moon et al. 1992) |
| Cyanobacterin | - | Algicide, herbicide, antibiotic | Nostoc linckia | (Gleason 1990; Gromov et al. 1991) |

| Name | Chemical Class | Activity | Source | Reference |
|---|---|---|---|---|
| Cyanobacterin | - | Antibiotic, algicide | Nostoc spp. | (Verpritskii et al. 1991) |
| Cyanopeptolins | Depsipeptide | Protease inhibitors | Microcystis spp. | (Martin et al. 1993; Jakobi et al. 1995) |
| Fisherellin | - | Allelotoxin | Fischerella musicola | (Gross et al. 1992) |
| Fontomumide | Alkaloid | - | Hapalosiphon fontinalis | (Moore et al. 1987) |
| Haplaindoles | Alkaloids | - | Hapalosiphon fontinalis | (Moore et al. 1984) |
| Hormothamnins | Cyclic undecapeptide | Cytotoxic, antimicrobial, antimycotic | Hormothamnione enteromorphoides | (Gerwick et al. 1989; Gerwick et al. 1992) |
| Hormothamnione | - | Cytotoxic | Hormothamnione enteromorphoides | (Gerwick et al. 1986) |
| Indolcarbazoles | - | Cytotoxic, antiviral | Nosctocaceae | (Knubel et al. 1990) |
| Insecticidal compounds | - | - | Oscillatoria agardhii | (Harada et al. 2000) |
| Ischerindole | Isonitrile | - | Fischerella musicola | (Park et al. 1992) |
| Laxaphycin | Cyclic undeca- or dodeca-peptides | Cytotoxic, antimicrobial, antimycotic | Anabaena laxa | (Frankmolle et al. 1992) |
| Lyngbyatoxins | Cyclic dipeptides | Tumour promoters | Lyngbya majuscula | (Fujiki et al. 1981) |
| Majusculamides | Heptacyclo-depsipeptides | Cytotoxic, antifungal | Lyngbya majuscula | (Marner and Moore 1977; Carter et al. 1984; Moore and Entzeroth 1988) |
| Malyngamides | - | - | Lyngbya majuscula | (Gerwick et al. 1987) |
| Malyngolide | - | Antibiotic | Lyngbya majuscula | (Cardelina et al. 1979) |

| Name | Chemical Class | Activity | Source | Reference |
|---|---|---|---|---|
| Malynic acid | Fatty acid | Cytotoxin | Lyngbya majuscula | (Cardelina and Moore 1980) |
| Microcolins | Peptide | Immuno-suppressant | Lyngbya majuscula | (Koehn et al. 1992) |
| Microcystilide | Depsipeptide | Cell differentiation promoter | Microcystis aeruginosa | (Tsukamoto et al. 1993) |
| Microginin | Linear pentapeptide | ACE inhibitor | Microcystis aeruginosa | (Okino et al. 1993) |
| Microviridins | Depsipeptide | Protease inhibitors | M. viridis | (Ishitsuka et al. 1990) |
| Mirabazoles | Alkaloids | Cytotoxins | Scytonema mirabile | (Carmeli et al. 1991) |
| Muscoride | Oxazole peptide alkaloid | - | Nostoc muscorum | (Nagatsu et al. 1995) |
| Nostocyclin | Depsipeptide | - | Nostoc spp. | (Kaya et al. 1996) |
| Nostophycin | Cyclic peptide | - | Nostoc spp. | (Fujii et al. 1999) |
| Oscillamide | Cyclic peptide | Chymotrypsin inhibitor | Oscillatoria agardhii | (Sano and Kaya 1995) |
| Oscillapeptin | - | Chymotrypsin and elastin inhibitor | Oscillatoria agardhii | (Shin et al. 1995) |
| Oscillatoxin | - | Toxin | Oscillatoria spp. | (Mynderse and Moore 1978) |
| Pahayokolide A | - | Antibiotic, cytotoxic | Lyngbya spp. (freshwater) | (Berry et al. 2004) |
| Polytoxin | - | - | Scytonema spp. | (Carmeli et al. 1990a) |
| Puwainaphycin | Cyclic peptide | Cardioactive | Anabaena spp. | (Moore et al. 1989) |
| Scyptolins | Depsipeptides | - | Scytonema hofmanii | (Matern et al. 2001) |

| Name | Chemical Class | Activity | Source | Reference |
|---|---|---|---|---|
| Scytophycins, tolytoxin | - | Cytotoxic, antimycotic | Scytonema pseudohofmanni | (Ishibash et al. 1986; Patterson and Carmeli 1992) |
| Tantazoles | Alkaloids | Cytotoxins | Scytonema mirabile | (Carmeli et al. 1990b) |
| Westiallamide | Cyclic hexapeptide | Cytotoxic | Westiellopsis prolifica | (Prinsep et al. 1992a) |