Review

Production of the neurotoxin beta-N-methylamino-L-alanine may be triggered by agricultural nutrients: An emerging public health issue

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ABSTRACT

Diverse taxa of cyanobacteria, dinoflagellates and diatoms produce β-N-methylamino-L-alanine (BMAA), a non-lipophilic, non-protein amino acid. BMAA is a neurotoxin in mammals. Its ingestion may be linked to human neurodegenerative diseases, namely the Amyotrophic lateral sclerosis/Parkinsonism dementia complex, based on epidemiological evidence from regions where cyanobacterial harmful algal blooms occur frequently. In controlled environments, cyanobacteria produce BMAA in response to ecophysiological cues such as nutrient availability, which may explain the elevated BMAA concentrations in freshwater environments that receive nutrient-rich agricultural runoff. This critical review paper summarizes what is known about how BMAA supports ecophysiological functions like nitrogen metabolism, photosyntheis and provides a competitive advantage to cyanobacteria in controlled and natural environments. We explain how BMAA production affected competitive interactions among the N_2-fixing and non-N_2-fixing populations in a freshwater cyanobacterial bloom that was stimulated by nutrient loading from the surrounding agricultural landscape. Better control of nutrients in agricultural fields is an excellent strategy to avoid the negative environmental consequences and public health concerns related to BMAA production.

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Contents

1. Introduction

The neurotoxin β-N-methylamino-L-alanine (BMAA), a non-protein amino acid that is a suspected causative agent of human neurodegenerative diseases, is produced by diverse cyanobacteria,

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dinoflagellates and diatoms (Cox et al., 2005; Lage et al., 2014; Réveillon et al., 2014). Evidence of the connection between BMAA and the Amyotrophic lateral sclerosis/Parkinsonism dementia complex was first documented in Guam, where local residents who consumed cycad flour and flying foxes containing BMAA had 100 times greater incidence of these neurological disorders than the global baseline (Cox and Sacks, 2002; Cox et al., 2016). Humans are exposed to BMAA through ingestion and dermal contact with contaminated water and food, or inhalation of dust containing BMAA, but the greatest environmental health risk is from cyanobacterial harmful algal blooms (CyanoHABs) because of their global occurrence (Huisman et al., 2018; Merel et al., 2013). This perspective is supported by eco-epidemiological modelling showing that sporadic Amyotrophic lateral sclerosis is associated with BMAA produced by CyanoHABs (Snyder et al., 2009; Torbick et al., 2014).

Most cyanobacteria could produce BMAA, whether they are plant symbionts, in mats growing in ponds and on sediments, or in biological soil crusts and surface soil (0–2 cm) (Cox et al., 2005; Jungblut et al., 2018; Metcalf et al., 2015; Richer et al., 2015). However, detection of BMAA production in CyanoHABs is alarming due to the increasing frequency, magnitude and duration of CyanoHABs in fresh water systems worldwide, especially in watersheds where nutrient loading occurs due to urban and rural activities (Huisman et al., 2018). In controlled studies, cyanobacteria produce BMAA in response to ecophysiological cues, including nutrient availability. We postulate that nutrients in agricultural runoff triggers BMAA production in CyanoHABs, but this requires nutrient loading to occur in the right proportions, at the right time and possibly in combination with other factors that induce BMAA production by cyanobacteria.

The objective of this critical review paper is to present evidence of the connection between nutrient loading from agricultural runoff and BMAA production in CyanoHABs in freshwater environments. We begin by discussing the metabolic and ecological functions of BMAA for cyanobacteria populations and the factors that trigger BMAA production. Then, we describe the known and hypothesized connections between nutrients in agricultural runoff and BMAA production by freshwater CyanoHABs. Finally, we discuss the opportunities and limitations of agricultural best management practices to reduce the environmental and public health risks associated with the cyanotoxin BMAA.

2. BMAA production and its ecophysiological role in cyanobacteria

Understanding BMAA synthesis and functions in cyanobacteria remains challenging, since it may exist as a free amino acid, be associated with or incorporated into protein, or complexed with metal ions (Cao et al., 2019). This section summarizes the factors influencing BMAA production and its ecophysiological role in cyanobacteria.

2.1. Factors contributing to BMAA production

Cyanobacteria produce several forms of BMAA through distinct biosynthesis pathways. Cyanobacteria could biosynthesize the free amino acid form (keto acid β-N-methylaminopyruvate) directly by methylation of free 2,3-diaminopropionic acid (DAP) or by enzymatic hydrolysis of BMAA associated with proteins (Downing et al., 2011; Tripathi and Gottesman, 2016). Alternatively, the cyanobacteria *Synechocystis* PCC6803 may biosynthesize BMAA through hydrolysis of a cyclic urea compound (Downing and Downing, 2016). The genetic basis for BMAA biosynthesis in the cycad-cyanobacteria symbiosis is associated with glutamate receptor-like genes (Brenner et al., 2003). Ongoing research into BMAA stereochemistry and molecular transcriptomics should improve understanding of BMAA biosynthesis pathways in cyanobacteria (Diaz-parga et al., 2018; Popova et al., 2018).

Like other cyanotoxins, the free amino acid form of BMAA probably exists in the nucleoplasmic region, thylakoid area, cell wall and sheath of cyanobacteria cells (Vega and Bell, 1967). It also associates with membrane, bound peptides or proteins in the cytoplasm (Faassen et al., 2016). After cyanobacteria biosynthesize BMAA, the BMAA molecule remains in the cell during its lifespan. Dead or damaged cyanobacteria cells lyse and release BMAA into the environment. Therefore, BMAA appearing in the environment originated from (a) *de novo* BMAA biosynthesis in the cell, and (b) BMAA released into the environment through cellular lysis (Pernil et al., 2015; Main et al., 2018).

Under nitrogen (N)-deficient conditions, both non-N_2-fixing and N_2-fixing cyanobacteria can synthesize BMAA (Monteiro et al., 2017). However, the non-N_2-fixing cyanobacteria are expected to produce more BMAA than N_2-fixing cyanobacteria in N-limited environments (Scott et al., 2014; Downing et al., 2011; Downing et al., 2012; Monteiro et al., 2017; Popova et al., 2018). N concentrations of 0–40 μM in the NH_4 and NO_3 forms trigger BMAA production by the non-N_2-fixing cyanobacteria are growing in a bloom and laboratory cultures (Table 1). In addition to *de novo* BMAA biosynthesis, cyanobacteria can absorb exgeneous BMAA from the environment (Berntzon et al., 2013; Downing et al., 2011). Absorbed BMAA could be biodegraded within the cell, or it could be re-released into the environment after cell death and lysis. In laboratory cultures, cyanobacteria populations are viable for about 30 days (Nizan et al., 1986), but the generation time could be as short as 7 days in CyanoHABs during summer months (Bidle and Falkowski, 2004) or as long as 90 days in biological soil crusts (Mugnai et al., 2018). Apoptosis, necrosis and senescence are the main forms of cell death (Bidle and Falkowski, 2004), followed by lysis of the plasma membrane by viral, enzymatic or osmotic mechanisms. Abiotic stressors that induce cellular lysis include nutrient stress due to excess/deficiency of phosphorus or iron (Bidle, 2016; Berman-Frank et al., 2004; Popova et al., 2018), salt stress (Ning et al., 2002), high light stress (Berman-Frank et al., 2007) and oxidative stress (Ross et al., 2006). In addition, biotic stress due to viral and bacteriophage infections, as well as predation from animal-like protists, flagellates and other microbiota, cause cellular lysis (Haraldsson et al., 2018).
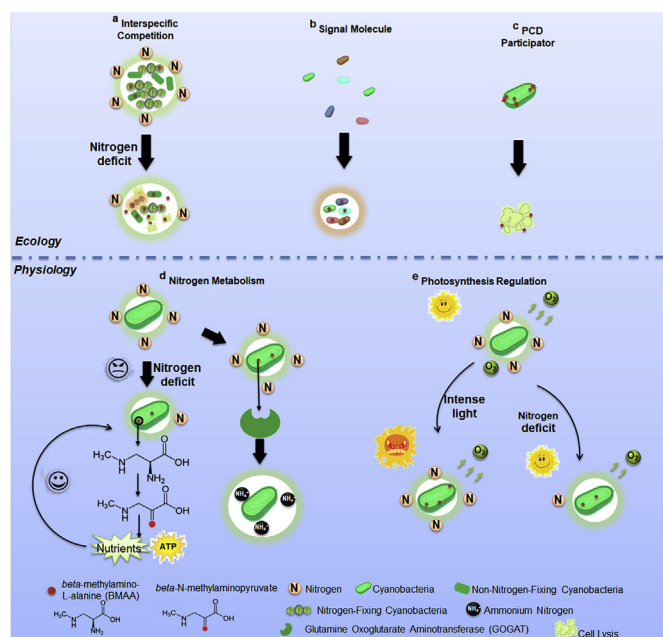
2.2. Ecophysiological role of BMAA

Since there is an energetic cost to synthesize cyanotoxins, including BMAA, there must be an evolutionary advantage for cyanobacteria that retained BMAA biosynthesis capacity. This molecule may ensure the organism's functional niche (ecological advantage) or improve its fitness (physiological efficiency). Based on the literature, we suggest three ecological roles and two physiological roles of BMAA for cyanobacteria (Fig. 1). Other ecophysiological functions of BMAA may be discovered in the future.

Interspecific Competition. N availabilty plays a critical role in the production of BMAA by cyanobacteria (Agawin et al., 2007; Downing et al., 2011; Monteiro et al., 2017). When the available nitrate concentration falls below 0.3–0.4 μM, N_2-fixing cyanobacteria initiate the N_2 fixing reaction, which is energetically costly, requiring 18 molecules of ATP and 8 low-potential electrons per molecule of N_2 fixed (Canfield et al., 2010; Ferber et al., 2004). This metabolic process requires P for energy and several elements (Fe, Mo, S, O) to build the electron-donating iron-molybdenum cofactor in nitrogenase, thereby depleting these essential nutrients from the environment.

Table 1
Production of β-N-methylamino-ʟ-alanine (BMAA) by non-N$_2$-fixing cyanobacteria in laboratory cultures as influenced by nitrogen.

Species	Nitrogen source	Nitrogen exposure (μM)	BMAA concentration (ng/g cells (dry weight))	Reference
Synechocystis J341	NaNO$_3$	1.8×10^3 μM NaNO$_3$	ND[a]	Scott et al. (2014)
		0	[b] The peak area of LC/MS detection of BMAA is 1.5×10^6	Downing et al. (2011)
Microcystis PCC7806	—	0	[b] The peak area of LC/MS detection of BMAA is 1.2×10^5	
	NH$_4$Cl	1000 μM NH$_4$Cl	ND[a]	
	NaNO$_3$	1000 μM NaNO3	ND[a]	
Microcystis aeruginosa	NaNO$_3$	1.76×10^3 μM NaNO$_3$	ND[a]	Fan et al. (2015)
		17.6×10^3 μM NaNO$_3$	ND[a]	
		52.8×10^3 μM NaNO$_3$	ND[a]	
Microcystis aeruginosa bloom	—	~0 μM Combined nitrogen	252	Scott et al. (2014)
	Nitrate	40 μM Combined nitrogen	34	
	Nitrite	>40 μM Combined nitrogen	ND[a]	
	Ammonia			

ND[a] = not detectable; [b] Peak area, as BMAA concentration was not quantified by the authors.

Fig. 1. Proposed ecological and physiological roles of β-N-methylamino-ʟ-alanine (BMAA) in cyanobacteria.

Under N-deficient conditions, both non-N$_2$-fixing and N$_2$-fixing cyanobacteria can synthesize BMAA (Cox et al., 2005; Main et al., 2018; Monteiro et al., 2017; Rodgers et al., 2018; Violi et al., 2019). However, the non-N$_2$-fixing cyanobacteria are expected to produce more BMAA than N$_2$-fixing cyanobacteria in N-limited environments. This statement is consistent with the observation that the non-N$_2$-fixing Microcystis aeruginosa had >7 times higher BMAA concentration in a reservoir with ~1 μM NO$_3$ than when the environment contained 40 μM NO$_3$ (Scott et al., 2014). Furthermore, N deprivation induced higher BMAA production in Synechocystis and Microcystis (non-N$_2$-fixing cyanobacteria) in laboratory experiments (Downing et al., 2011; Downing et al., 2012; Popova et al., 2018). In contrast, there was 4-fold less BMAA produced by Nostoc sp. (N$_2$-fixing cyanobacteria) in a N-free cultures than in N-containing medium (the actual N concentration in the culture media is not reported in the paper) (Monteiro et al., 2017). Together, these reports suggest that non-N$_2$-fixing cyanobacteria are the dominant BMAA producers in N-deficient conditions.

The BMAA produced by non-N$_2$-fixing cyanobacteria under N starvation could be absorbed by N$_2$-fixing cyanobacteria and inhibit their nitrogenase activity, thus altering the competition interactions among non-N$_2$-fixing and N$_2$-fixing cyanobacteria (Berntzon et al., 2013; Popova et al., 2018). For example, non-N$_2$-fixing Microcystis outcompeted the N$_2$-fixing Aphanizomenon when the soluble N concentration was 0.5−2 mg N/L in the freshwater Lake Mendota, located in Wisconsin, USA (Beversdorf et al., 2013). The competitive advantage permitted the non-N$_2$-fixing Microcystis population to increase from 10^3 cells/mL to 10^6 cells/mL, while the population of N$_2$-fixing Aphanizomenon declined from 10^6 cells/mL to 10^5 cells/mL from July to September (Beversdorf et al., 2013). Although these authors did not evaluate BMAA production by the Microcystis population, we posit that if the non-N$_2$-fixing cyanobacteria produced BMAA, it could have two benefits for their population. First, BMAA kills some of the N$_2$-fixing cyanobacteria and nutrients released from their lysed cells can be recycled by the non-N$_2$-fixing cyanobacteria population. Second, BMAA blocks nitrogenase activity and constrains the growth of N$_2$-fixing cyanobacteria, thereby reducing their population size and liberating resources such as space and oxygen needed by the non-N$_2$-fixing cyanobacteria population.

We also know that N$_2$-fixing cyanobacteria produce BMAA and can have a high BMAA concentration in laboratory cultures and CyanoHABs (Cox et al., 2005; Main et al., 2018). However, we do not know whether the high BMAA concentration in N$_2$-fixing cyanobacteria is due to in vivo synthesis of the molecule, or whether the BMAA was originally produced by another organism and assimilated by the N$_2$-fixing cyanobacteria population. How environmental conditions, particularly N availability, affect BMAA production by N$_2$-fixing cyanobacteria still remains to be understood. We believe that cyanobacteria have physiological adaptations that allow them to bioaccumulate and sequester BMAA in their organelles, to avoid toxic effects, although we do not know the threshold for BMAA tolerance within organelles. This possibility offers hope for the development of genetic and biochemical therapies to treat humans and mammals exposed to BMAA. It could also explain the co-existance of non-N$_2$-fixing and N$_2$-fixing cyanobacteria in freshwater environments, despite the ability of both groups to produce lethal BMAA. Doubtless, each group has adapted to the selective pressure of the BMAA molecule and developed strategies to maintain their functional niche after millenia of co-evolution.

Signal Molecule. BMAA has chemical characteristics that are analogous to other signal molecules produced by prokaryotes such as high hydrophility (LogK$_{ow}$ = -4.00), molecular weight of 118 Da and diffusion coefficient of 0.78 (Diaz-parga et al., 2018). Most cyanobacteria taxa seem to produce BMAA, and it is postulated to be a signal molecule responsible for communication among cyanobacteria species (Cox et al., 2005). Other non-protein amino acids that are chemically similar to BMAA, such as γ-Aminobutyric acid

(GABA), accumulate rapidly in plants under stress and initiate defense pathways against drought and insect herbivory (Bown and Shelp, 2016). If BMAA is a GABA analogue, it may regulate the cyanobacteria metabolism in response to stress or be an adaptive response to mitigate stress, but this still remains to be determined.

PCD (Programmed Cell Death) Participator. Like other prokaryotes, cyanobacteria initiate PCD under stressful environmental conditions. The genetic basis for PCD are the metacaspases, which initiate targeted protein degradation in the apoptotic PCD pathways with high catalytic efficiencies and strict substrate specificities (Asplund-Samuelsson et al., 2016). Phylogenetic analysis of N_2-fixing cyanobacteria with 16S RNA analysis revealed metacaspase orthologues, which suggests that cyanobacteria initiate PCD when they encounter stressful conditions (Bidle and Falkowski, 2004; Bar-Zeev et al., 2013; He et al., 2016; Ross et al., 2006). The presence of exogenous BMAA is an indication that cyanobacteria cells are dying and being lysed by abiotic and biotic stressors, described in section 2.1 (Bishop et al., 2018; Monteiro et al., 2017). Thus, an increase in exogenous BMAA concentration could induce the expression of metacaspase genes and initiate PCD as a negative feedback to control the size of cyanobacteria populations.

Nitrogen Metabolism. As described previously, BMAA biosynthesis is associated with cellular N stress (Holtcamp, 2012; Popova et al., 2018; Downing et al., 2011). Cultures grown under N starvation conditions (<10 μM) may produce BMAA to initiate the ionotropic glutamate receptors (iGLuRs) and thus activate glutamate receptor cation (Ca^{2+}) channels, which controls Ca^{2+} movement and maintains the integrity of cellular membranes (Berntzon et al., 2013; Brenner et al., 2000). Another possible role for BMAA is to initiate the incorporation of Ca^{2+} into the carbon skeleton of 2-oxoglutarate after enzymatic reduction (Weiland et al., 2015). Although it seems counter-intuitive to use limited N resources to synthesize a non-protein amino acid like BMAA, there is evidence that the primary amino-N group in BMAA can be redistributed to glumate and glutamine via transamination of the enzyme glutamine synthetase-glutamine oxoglutarate aminotransferase (GOGAT) (Martın-Figueroa et al., 2000; Downing et al., 2011). Therefore, BMAA has important physiological functions that maintain the integrity of cyanobacteria cells under N starvation conditions. This implies that cyanobacteria have cellular mechanisms to reassimilate the amino-N portions of the BMAA molecule once the protective glutamate pathways are initiated.

Photosynthesis regulation. Cyanobacteria are photosynthetic organisms that must protect their photosynthetic apparatus from damage by photooxidation, and this could be assisted by the BMAA molecule. First, BMAA acts as a glutamate receptor agonist that alters the cell membrane potential of the model plant *Arabidopsis*, thus affecting the light signal transduction (Brenner et al., 2000). The glutamate receptor of *Arabidopsis* is highly homologous with the same receptor in the cyanobacteria *Synechocystis* sp. (Chen et al., 1999). It is thought that BMAA regulates oxygenic photosynthesis by blocking light signal transduction to protect cyanobacteria from oxidative damage when photosynthesis occurs under high light intensity and limited N availability (Downing et al., 2015). Second, BMAA might regulate chlorophyll *a* activity to avoid its photooxidation. Since BMAA is produced under N starvation conditions that induce chlorosis and the degradation of photosynthetic pigments, it would be logical for BMAA to protect pigments used in the xanthophyll cycle to dissipate light radiation before it damages the chloroplast, or to inhibit the activity of chlorophyll *a*, as proposed by Downing and Downing (2016) and Berntzon et al. (2013).

3. Contribution of agricultural nutrients to BMAA production in freshwater environments

Virtually every CyanoHABs in a freshwater environment is associated with elevated nutrient concentrations in the waterbody. The exponential growth that is characteristic of an algal bloom will not occur if the cyanobacteria are lacking in phosphorus (<0.2 mg total P/L) and N (<0.8 mg total N/L) (Paerl et al., 2011; Xu et al., 2014; Schindler et al., 2008). Nitrogen may originate from biogeochemical cycling within the aquatic system, but also enters as runoff from upstream terrestrial environments, intrusion of N-rich groundwater and via atmospheric deposition (Gruber and Galloway, 2008; Elser and Bennett, 2011). As an example, we critically review the specific case of the eleventh-largest freshwater lake (by area) in the world, Lake Winnipeg in Manitoba, Canada. In Lake Winnipeg, the total N budget is 96, 000 ton/yr, where 29% of N comes from in-lake processes and the remaining 71% is derived from sources outside the aquatic system (Board, 2006). At least 49% of the exogeneous N is delivered in runoff from the surrounding agricultural land (Rattan et al., 2017). Agricultural runoff is responsible for N levels of up to 18.5 mg total N/L and phophorous levels as high as 4 mg total P/L, which simulate and sustain the high-biomass bloom in excess of 20 μg cells/L in Lake Winnipeg (Braun, 2007; Rattan et al., 2017; Paerl et al., 2011; Hamilton et al., 2016; Michalak et al., 2013). Agricultural activities contribute to nutrient loading because fertilizer, manure and other nutrient-rich materials applied for crop production release dissolved and particulate-associated nutrients that are susceptible to transport from farm fields (Li et al., 2018; Castellano et al., 2019; Whalen et al., 2019). However, the N transfer from agroecosystems to downstream rivers and lakes is seasonally variable because it is influenced by climatic conditions, hydrologic processes within the watershed and agricultural management. Dissolved and particulate nutrients are readily transported during snowmelt in spring, and after rainfall events in the early growing season that have enough intensity and/or duration to generate overland flow, and these nutrient sources are associated with the emergence and exponential growth phases in CyanoHABs (Chen et al., 2010; Schneider et al., 2019; Zhang et al., 2012; Smith et al., 2007). Nutrient transfers decline during late summer to late fall because rainfall is more sporadic at this time of year, so agricultural fields are drier and receiving little or no fertilizer as crops mature and are harvested. The late summer to late fall period is a time when CyanoHABs go into decline and collapse (Reichwaldt and Ghadouani, 2012).

The dynamics of CyanoHABs depend on many factors, including N loading from agroecosystems, but we hypothesize that relationships exist between the CyanoHABs growth phase, BMAA concentration and N loading in Lake Winnipeg. From emergence to the bloom phase, the BMAA concentration ranged from undetectable to low, and this increased approximately 20-fold to as much as 306 μg BMAA/L during the decline and collapse phases, in late fall (Pip et al., 2016; Bishop et al., 2018; Main et al., 2018; Zguna et al., 2019). We posit that agricultural runoff triggers BMAA production because it influences the N entering the lake at different phases of bloom. We can evaluate these relationships in Lake Winnipeg because data exists on the temporal variation in BMAA production and CyanoHABs, as well as the N loading into this lake. The next sections discuss the known and hypothesized connections between the recurrent CyanoHABs in Lake Winnipeg and agricultural activities in its 982,900 km^2 watershed, which includes three US states (North Dakota, South Dakota and Minnesota) and four Canadian provinces (Alberta, Saskatchewan, Ontario and Manitoba).

3.1. Lake Winnipeg, a freshwater lake where BMAA is produced by CyanoHABs

Detection of BMAA production in CyanoHABs was reported in British freshwater lakes and brackish waterbodies (Metcalf et al., 2008), the Baltic Sea (Jonasson et al., 2010), several freshwater environments in South Floria (Brand et al., 2010), Lake Taihu, China (Jiao et al., 2014), Lake Houston, the US (Holtcamp, 2012), Thau lagoon, French Mediterranean Sea (Réveillon et al., 2015) and Lake Winnipeg, Canada (Bishop et al., 2018; Pip et al., 2016). The specific example of Lake Winnipeg, Canada is compelling because this freshwater environment has experienced regular CyanoHABs since the late 1990s due to anthropogenic forces, primarily agricultural activities.

Lake Winnipeg is located in the cold humid temperate region of Manitoba, Canada and covers an area of 24,514 km^2, with two distinct basins, the South basin and the North basin (Wassenaar and Rao, 2012; Zhang and Rao, 2012). The CyanoHABs in this lake often cover thousands of square kilometers (Benoy et al., 2016). From 2002 to 2011, extensive blooms covered as much as 93% of the lake surface (Zhang and Rao, 2012; Binding et al., 2018). This represents a 5-fold increase in nuisance blooms of heterocystous cyanobacteria from the 1990s (Wassenaar and Rao, 2012).

In 2016, BMAA was present in about 25% of CyanoHABs in Lake Winnipeg (Bishop et al., 2018; Pip et al., 2016). Temporally, the BMAA production occurrred during the cyanobacterial bloom forming-season from early summer to late fall. We do not know what cyanobacteria are responsible for BMAA production in Lake Winnipeg, but BMAA could be associated with the toxic non-N_2-fixing cyanobacteria, such as *Planktothrix* and *Microcystis*. In the past decade, these genera have emerged as co-dominant populations together with the N_2-fixing cyanobacteria *Aphanizomenon* and *Dolichospermum*, which historically dominated the CyanoHABs. This widespread community-level change in CyanoHABs was attributed to the elevated N and phosphorus concentrations in lakes (Kling et al., 2011; McKindles et al., 2019). Furthermore, phosphorus-rich lakes that receive exogenous N inputs can see a 500% increase in cyanobacteria production and toxicity (Leavitt et al., 2006; Donald et al., 2011; Vogt et al., 2017). Therefore, temporal variation in BMAA production may be due to the emergence of toxic non-N_2-fixing cyanobacteria within the CyanoHABs (Pip et al., 2016), but a simpler explanation may be that BMAA production in this lake is responding to N availability, a major driver of BMAA production in controlled studies.

3.2. Lake Winnipeg, a freshwater lake where BMAA production is associated with agricultural nutrient loading

Lake Winnipeg's biggest problem stems from its large watershed, the high drainage to surface area ratio and the change in surrounding land use (Board, 2006; Benoy et al., 2016). Agriculture expansion occurred throughout the 20th century, particularly in the southern region of the Lake Winnipeg watershed. From 1990 to 2010, there was an intensification of hog production, more annual crop production and overall increase in livestock density (Bunting et al., 2011; Liu et al., 2014). At the same time, much of the post-glacial terrain was systematically drained through the creation of surface ditches and channels to accelerate drainage on agricultural land in southern Manitoba (Rattan et al., 2017). This also involved filling or draining wetlands to expand agricultural production (Schindler et al., 2012). The SPAtially Referenced Regressions on Watershed attributes (SPARROW) model indicates that about 65% of the total phosphorus load and approximately 75% of the total N load entering Lake Winnipeg originated from agricultural sources (Benoy et al., 2016). Approximately 7900 t phosphorus/year and 96

000 t N/year enter the watershed, primarily during snowmelt and spring runoff events (McCullough et al., 2012; Schindler et al., 2012).

The N concentration in Lake Winnipeg varies seasonally and corresponds to the loading pattern of agricultural nutrients (Schindler et al., 2012; Bunting et al., 2016). The highest N concentrations are recorded in late spring and summer months (Mayer and Wassenaar, 2012; Soto et al., 2019). From late summer to fall, nutrient loading from agricultural land is limited because fertilizer is not applied at the pre/post-harvest stage and there are fewer rainfall events that could induce N loss from agroecosystems. During development of the cyanobactrial bloom, the in-lake N concentration declines to <0.1 mg total N/L in late autumn (Mayer and Wassenaar, 2012; Pip et al., 2016). Furthermore, there is spatial variability in the NO_3 concentrations of Lake Winnipeg. The South basin receives about 69% more of the N load than the North basin in April and May, prior to the emergence and bloom phases of CyanoHABs (Environment and Climate Change Canada (2016)). By early July, the South basin becomes dominated by several non-N_2-fixing *Microcystis* and *Planktothrix* (Kling et al., 2011; McKindles et al., 2019). In an average flow year, nutrients in South basin are transmitted to the North basin after two or three months, in time to support the bloom that peaks in summer in both basins (Zhang and Rao, 2012; Binding et al., 2018). Consequently, the non-N_2-fixing cyanobacteria begin to experience N starvation during late summer and autumn in both basins (Bishop et al., 2018; Orihel et al., 2012). In-lake N dynamics are negatively related to the BMAA concentration (Pip et al., 2016; Pick, 2016; Vo Duy et al., 2019), which is expected to be lowest in the early summer (bloom emergence) and increasing from summer to autumn, with the peak BMAA concentration occurring just before bloom collapse (Fig. 2). Overall, the allochthonous agricultural nutrients may trigger BMAA production by influencing the composition of potentially toxic cyanobacteria species and the N level in Lake Winnipeg.

4. Controlling nutrients in agricultural fields to reduce human health risks from BMAA production in CyanoHABs

Detection of BMAA in freshwater lakes, many of which are drinking water sources, is an emerging public health issue (Craighead et al., 2009; Esterhuizen and Downing , 2008). Compared to other environmental sources, the BMAA concentration in freshwater lakes is high and represents an important exposure pathway (Table 2). Spatial analysis of Amyotrophic lateral sclerosis cases and lakes with a history of cyanobacterial blooms in New Hampshire revealed that people living within 1 km of cyanobacteria-contaminated lakes had a 2.3 times greater risk of developing Amyotrophic lateral sclerosis, and inhabitants of Lake Mascoma had up to 25 times greater risk of Amyotrophic lateral sclerosis than the general population (Caller et al., 2009). Relatively low exposure to BMAA is damaging, based on *in vitro* studies showing that BMAA causes selective motor neuron demise at concentrations as low as 30 μM (Rao et al., 2006) and damages motor neurons at concentrations of 10 μM (Lobner et al., 2007). Still, BMAA needs to be understood as a chronic neurotoxin because it binds with proteins and has a long latency period before the proteins degrade and slowly release free BMAA into human brain tissues (Holtcamp, 2012). The public health risk from long-term exposure to BMAA in freshwater environments should not be underestimated.

4.1. Managing agricultural nutrients to prevent CyanoHABs and the associated BMAA production

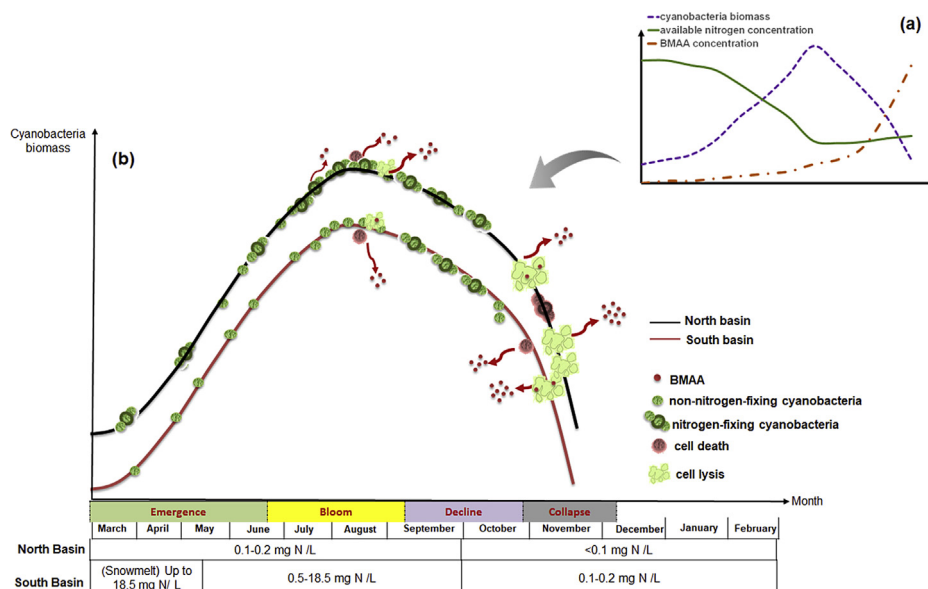Since BMAA production occurs during the CyanoHABs collapse

Fig. 2. Hypothesized relationship among available nitrogen concentration, cyanobacteria biomass and β-N-methylamino-L-alanine (BMAA) production (a) and relationship between BMAA production and development of cyanobacterial harmful algal blooms composed of the non-N_2-fixing cyanobacteria and N_2-fixing cyanobacteria in the North basin and South basin of Lake Winnipeg, Canada (based on CyanoHABs dynamics reported by Manitoba Sustainable Development and Environment and Climate Change Canada (2012, 2016) (b).
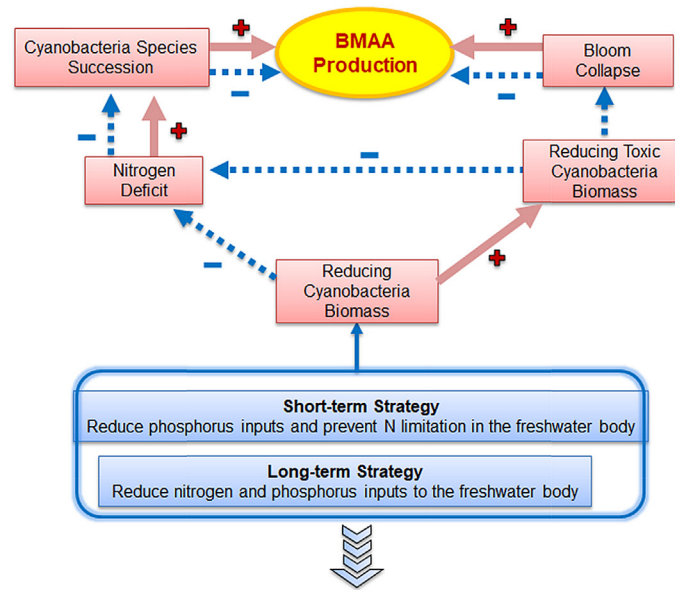
Table 2
Human exposure pathways to environmental sources of β-N-methylamino-L-alanine (BMAA).

Exposure pathway	Environmental source	Sampling location	Concentration (µg/g DW)	Concentration (µg/ L water)	Reference
Ingestion	Cycad flour	Guam, USA	40−169	−	Chen and Banack (2009)
	Shark fin	South Florida	144−1836	−	Mondo et al. (2012)
	Shark cartilage dietary supplements	South Florida	86−265	−	Mondo et al. (2012)
	Fa cai Nostoc soup	China	[a]ND-0.7	−	Roney et al. (2009)
	Algae dietary supplements	Pacific/Hawaii/Klamath Lake	Detectable	−	Roy-Lachapelle et al. (2017)
	Spirulina natural health products	Health food store in Canada	0.01−0.74	−	Faassen et al. (2009)
	Spirulina powder from commercial raw ingredient producers	N/A	0.01−0.07	−	Baker et al. (2018)
	Aphanizomenon flosaquae dietary supplements	Klamath Lake	~0.04	−	Roy-Lachapelle et al. (2017)
Inhalation	Biological crust	Gulf region/Qatar	Detectable		(Cox et al., 2005; Richer et al., 2015; Metcalf et al., 2015)
Oral/dermal contact	Water	Nebraska lakes	−	1.8−24.5	Al-Sammak et al. (2014)
		Lake Winnipeg, Canada	−	~1.0	Pip et al. (2016)
	Cyanobacteria	Lake Winnipeg, Canada	4.1−22.5	−	Bishop et al. (2018)
		Baltic Sea	0.001−0.015	−	Jonasson et al. (2010)
		Freshwater impoundments (Southern Africa)	0−2757	−	(Esterhuizen and Downing, 2008) (Esterhuizen and Downing, 2008)
		Lake Taihu, China	2.0−7.1	−	Jiao et al. (2014)
		Portuguese estuaries	0.04−63	−	Cianca et al. (2012)
		Multiple water bodies (Eastern Australia)	[a]ND~ 47.26	−	Main et al. (2018) Main et al. (2018)
	Urban waters (cyanobacteria bloom)	Dutch	Maximum 42	−	(Faassen et al., 2009)
	Untreated water (Drinking water reservior)	British waterbodies	Maximum 48	Maximum 231	Metcalf et al. (2008)

[a] ND = not detectable; LD$_{50}$ = 10 µg/L (fish larvae Danio rerio); 1500−5000 µg/L (brine shrimps Artemia salina); 5000 µg/L (the ciliate Nassula Sorex); ED$_{50}$ = 1430−1604 µM (human neurons).

phase, and is fueled by N availability during the entire bloom, the most efficient way to eliminate BMAA production in freshwater environments is to prevent CyanoHABs. This will involve preventative measures from multiple anthropogenic actors that contribute to N loading into vulnerable watersheds, due to the influence of N availability on cyanobacteria species succession and CyanoHABs collapse (Fig. 3). Agricultural best management practices that control the diffuse sources of nitrogen and phosphorus will be

critical, and these focus on controlling the transport processes and sources of excess nutrients. As illustrated in Fig. 3, interventions that enhance natural attenuation processes in water and solute transport pathways, as well as those that constrain the rate and time that N and phosphorus are applied to agricultural fields, are two critical ways to reduce N loading to freshwater bodies (Hamilton et al., 2016). End-of-field treatments with buffer strips, bioreactors and wetland restoration should be implemented to

Management	Process controlled	Practices	Impact on nutrient loss		Reference
			N	P	
Transport management	Surface runoff Subsurface runoff Leaching	Buffer strips	↓	↓	(Schoumans et al., 2014)
		Wetland preservation, restoration or reconstruction	↓	↓	(Paerl et al., 2016)
		Bioreactors	↓	↓	(Husk et al., 2017; Husk et al., 2018; Rasouli et al., 2014)
		Subsurface drainage system	↑	↓	(Kopacek et al., 2013; Michaud et al., 2019)
Source management	Manure storage	Lagoon, impermeable storage, barnyard runoff control	↓	↓	(Sharpley et al., 2007)
	Manure volume	Compost, transport excess out of the watershed			(Sharpley et al., 2007)
	Manure treatment	Add alum to reduces NH_3 loss and P solubility Flyash, Fe oxide or gypsum to reduce P solubility	↓	↓	(Sharpley et al., 2007)
	Manure application rate	Rate chosen to meet, but not exceed, crop needs	↓	↓	(Sharpley et al., 2007)
	Application timing	Growing season only, split application to synchronize N inputs with N-demanding growth stages	↓	↓	(Rasouli et al., 2014)
		Pre-sidedress soil NO_3-N test	↓	Neutral	(Rasouli et al., 2014)
	Application method	Soil P testing	Neutral	↓	(Shigaki et al., 2006)
		Subsurface injection (reduce N and P loss in runoff)	↑	↓	
	Crop management	Agroforestry systems, including short-rotation woody crops Biomass / bioenergy crops	↓	↓	
		Crop rotation or intercropping	↓	↓	(Rasouli et al., 2014; Wang et al., 2019)
		Keep soil surface covered by retaining crop residues / planting cover crop	↓	↓	

Fig. 3. Agricultural best management practices with potential to reduce β-N-methylamino-ʟ-alanine (BMAA) production by cyanobacterial harmful algal bloom (Husk et al., 2017, 2018; Kopacek et al., 2013; Michaud et al., 2019; Paerl et al., 2016; Rasouli et al., 2014; Schoumans et al., 2014; Sharpley et al., 2007; Shigaki et al., 2006; Wang et al., 2019).

slow hydrologic processes and capture nutrients before they enter the freshwater system. Precision agriculture approaches that combine remote sensing with judicious fertilizer use should prove effective in delivering N, phosphorus and other nutrients to agricultural fields in the quantities needed by crops during the growing season. Fall fertilization should be strongly discouraged since crop nutrient demand is low in autumn and the residual nutrients are susceptible to loss during winter and early spring, when most of the agricultural runoff occurs in cold humid temperate regions of the world. In the short-term, we cautiously suggest that one strategy to reduce BMAA production could be to avoid N starvation of the non-N_2-fixing cyanobacteria. This would be accomplished by inhibiting the growth and biomass accumulation of cyanobacteria by controlling the P input, and adding N to prevent the *de novo* BMAA production by the N limited non-N_2-fixing cyanobacteria (Fig. 3). This possibility needs to be verified experimentally before attempting any intervention in freshwater bodies, as it is simplistic to assume that N concentrations in the lake are the sole trigger of BMAA production in CyanoHABs.

5. Conclusion

This synthesis suggests reasons why cyanobacteria have evolved BMAA biosynthesis as a cellular function, and discusses the environmental stimuli that induce BMAA production. For non-N_2-fixing cyanobacteria populations, BMAA production gives them a competitive advantage and guarantees their co-existence with N_2-fixing cyanobacteria. Seasonal nutrient loading from agricultural land triggers and increases the production of BMAA by increasing the biomass of toxic cyanobacteria and altering the N availability in the freshwater environment. However, most of current understanding about BMAA production in cyanobacteria is still based on controlled laboratory work. Most field studies did not monitor the relationship between N availability and BMAA production, which makes it difficult to compare the lab and field work. Long-term monitoring is needed to confirm the relationship between agricultural nutrients, CyanoHABs and BMAA production. For instance, it is of utmost importance to identify the role of N availability on BMAA production in freshwater environments. Understanding the patterns of N loading from agricultural land along with the change in BMAA concentration, cyanobacterial community dynamics and toxicity will eventually lead to more efficient agricultural management plans for preventing BMAA. Dual control of phosphorus and N inputs from agricultural land, as well as measures to limit the N recycling in freshwater could be the optimal strategies to inhibit the growth of toxic cyanobacterial strains and control BMAA production.

BMAA is associated with acute and chronic neurotoxicity in humans leading to disorders in the Amyotrophic lateral sclerosis/ Parkinsonism dementia complex that are costly and burdensome for individuals, families and the health care profession. Reducing human health risk from BMAA production in CyanoHABs will require close collaboration between biochemists, hydrologists, ecologists, agronomists and policy makers to deal with this global problem. Public health officials must be attentive to the fact that BMAA is produced in CyanoHABs, which are occurring more frequently, with longer duration and larger size, due to global warming and more anthropogenic nutrient loading in waterways around the world (Merel et al., 2013; Reichwaldt and Ghadouani, 2012). Part of the solution will be more aggressive strategies to stop agricultural nutrient loading in lakes. We need policies that clearly state the responsibilities of various stakeholders, as well as financial commitments from governments and citizens to manage eutrophic watersheds. We need to use our knowledge of cyanobacteria biology to control their populations and to prevent

CyanoHABs that produce BMAA, so we can preserve the freshwater environments that are critically connected to our long-term public health.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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