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Review

REVIEW

Excitatory amino acid β-*N*-methylamino-L-alanine is a putative environmental neurotoxin

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Abstract: The amino acid β-*N*-methylamino-L-alanine (L-BMAA) has been associated with the amyotrophic lateral sclerosis/parkinsonism-dementia complex in three distinct western Pacific populations. The putative neurotoxin is produced by cyanobacteria, which live symbiotically in the roots of cycad trees. L-BMAA was thought to be a threat only to those few populations whose diet and medicines rely heavily on cycad seeds. However, the recent discovery that cyanobacteria from diverse terrestrial, freshwater, and saltwater ecosystems around the world produce the toxin requires a reassessment of whether it poses a larger health threat. Therefore, it is proposed that monitoring L-BMAA levels in cyanobacteria-contaminated water supplies might be prudent.

Keywords: β-*N*-methylamino-L-alanine; neurodegenerative diseases; neurotoxicity; environmental toxin.

CONTENTS

1. INTRODUCTION

It has been well established that cyanobacterial and other environmental toxins cause and/or promote the development of a vast variety of diseases and

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disturbances in both animals and men.[1–3] Environmentally available excitatory amino acids are a good example. When ingested, or otherwise introduced into an organism, they can induce numerous disturbances of the nervous system. One of the excitatory amino acids that has received a lot of attention lately is *β-N*-methylamino-alanine (BMAA).

β-N-Methylamino-alanine is a highly reactive, low molecular weight amino acid (MW 118 g mol^{-1}) with unusual chemistry, originating as a result of its 2-amino groups being only partially ionized under physiological conditions.[4] It was first isolated by Vega and Bell[5] in 1967 as a result of an effort to isolate a causative agent of the amyotrophic lateral sclerosis/Parkinsonism-dementia complex of the Western Pacific (ALS/PDC).

The Western Pacific amyotrophic lateral sclerosis/Parkinsonism–dementia complex has been reported in three genetically and ethnically distinct population groups residing in Guam (Chamorros of the Marianas Islands), Japan (Japanese residents of the Kii Peninsula, Honshu Island) and New Guinea (indigenous people of South West Papua or Irian Jaya, Indonesia). This disease presents a spectrum of neurological disorders with unusually high incidence, characterized by features of ALS, Parkinsonism, dementia, or a combination of these.[6]

BMAA is proposed to contribute to ALS/PDC based on its presence in Cycad seeds which have been singled out as the strongest epidemiological link to the disease, and constitute a dietary or medicinal item in all the afflicted populations. It is noteworthy that BMAA passes the blood–brain barrier,[7,8] and its bioavailability in primates, when orally administered, is 80 %.[9]

Although the role of BMAA in human neurodegenerative disease is still debated,[10,11] a series of investigations both *in vitro* and *in vivo* has unequivocally established that the amino acid is indeed a neurotoxin.

2. THE BMAA NEUROTOXICITY

The first report describing BMAA-induced neurotoxicity was made the same year the amino acid was first isolated. Bell and colleagues presented the results at the 5th Cycad Conference in 1967. They administered natural and synthetic BMAA intraperitoneally to chicks. The symptoms produced by both natural and synthetic BMAA were general unsteadiness in standing, followed by loss of ability to extend the legs and stand erect. The head was often bend down, the feet were no longer held straight, and the chicks would often fall over and were unable to get up. They showed head circling movements and head retraction. Higher doses of BMAA increased the proportion of chicks affected, decreased the period between injection and the appearance of toxic symptoms and lengthened the period of intoxication.[12]

The landmark paper showing the neurotoxic effects of BMAA in primates was published in 1987 by Spencer and colleagues.[13] One-year-old male cyno-

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molgus monkeys received by gavage varying doses of L-BMAA (100–315 mg kg^{-1} daily for up to 12 weeks). They were clinically and neuropathologically examined, and also evaluated neurophysiologically. Neurological deficits appeared insidiously after 2–12 weeks and signs of motor neuron dysfunction developed symmetrically or asymmetrically. Clinical and electrophysiological signs of motor deficit preceded the appearance of physical alterations in the corresponding areas of the CNS. The regional susceptibility to L-BMAA showed a gradation from motor cortex to spinal cord to substantia nigra (from most affected to least affected). In this study, Spencer *et al.*[13] showed clinical, neurophysiological and neuropathological evidence that L-BMAA induces a primate motor system disorder with involvement of the upper and lower motor neurons and the extrapyramidal system.

Numerous investigations that followed confirmed the neurotoxic properties of BMAA. It was shown that in rats, BMAA causes acute motoric and behavioral deficits,[14–18] signs of cerebellar dysfunction,[14,15] and hyperexcitability with body shakes, convulsions and epileptiform activity on EEG.[19,20] Neuropathologically, BMAA has caused postsynaptic vacuolization and neurodegeneration of cortical,[21] spinal cord,[22] and hippocampal[23] neurons in mice, as well as neurodegeneration of cerebellar,[14,24] and monoaminergic[16,25] neurons in rats.

In a recent investigation, Karlsson *et al.*[26] studied the transfer of BMAA to fetal and neonatal brains and the effects of BMAA on the development of behavioral characteristics in rodents. The study revealed transplacental transfer of (3)*H*-BMAA and a significant uptake in fetal mouse brain. The radioactivity was specifically located in the hippocampus, striatum, brainstem, spinal cord and cerebellum of 10-day-old mice. BMAA treatment on postnatal days 9–10 induced acute alterations in the behavior of neonatal rats, such as impaired locomotive ability and hyperactivity. The observed behavioral changes also suggested possible cognitive impairment.[26] The same group reports that rats treated with BMAA during the neonatal period displayed acute but transient motoric disturbances, long-term learning impairments and failed to show habituation at a juvenile age.[27]

Santucci and coworkers[28] provided further evidence supporting a direct causal link between L-BMAA and neuronal damage. The authors studied the effect of L-BMAA on cell viability *in vivo* by measuring the electrophysiological activity of mouse retinal neurons by electroretinography recordings. Intra-ocular injections of L-BMAA selectively reduced the amplitude of the *b*-wave, without affecting either the *a*-wave amplitude or the *a*- and *b*-latencies. Death of retinal cells was evidenced by histology on retina sections, caspase 3 activation, incurporation of propidium iodide and production of reactive oxygen species. Co-injection of the specific NMDA antagonist, MK-801, significantly protected the retinal neurons from L-BMAA/NMDA-induced apoptosis.[28]

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Finally, BMAA exhibited toxicity in various aquatic animal species, including zebra fish (*Danio rerio*), brine shrimp (*Artemia salina*) and the protozoan *Nassula sorex*, with the toxic responses presented as clonus convulsions and abnormal spinal axis formation (*D. rerio*), loss of phototaxis (*A. salina*) and mortalities (all species),[29] while dietary intake of BMAA reduced the lifespan as well as the neurological functions of *Drosophila melanogaster* flies.[30]

Of particular relevance to human health, in two independent laboratories where blinded brain tissue samples were tested, both found BMAA in patients who had died of neurodegenerative disease but not in patients who died of causes unrelated to neurodegeneration.

Murch *et al*.[31] showed that BMAA occurs in the brains of Guamanians dying of ALS/PDC (average concentration 627 μg g^{-1}, 5 mM) but not in control brains. Moreover, they reported that BMAA was present in the brain tissues of North American patients who had died of Alzheimer's disease (average concentration 95 μg g^{-1}, 0.8 mM).[31] Although Snyder *et al.*,[32] using a different HPLC method and other assay techniques, were unable to reproduce the findings of Murch *et al.*,[31] Pablo and colleagues,[33] using the original techniques of Murch and coworkers,[31] recently confirmed the presence of protein-bound BMAA in postmortem brain specimens taken from neuropathologically confirmed cases of 13 ALS, 12 Alzheimer's disease (AD), and 8 Huntington's disease North American patients. The authors reported the presence of BMAA in concentrations exceeding 100 μg g^{-1} in patients who had died with sporadic AD and ALS but not in the brains of non-neurological controls or Huntington's disease patients.[33]

3. MECHANISMS OF BMAA NEUROTOXICITY

The greatest initial insight into the mechanisms of BMAA neurotoxicity was provided by electrophysiological studies. In a breakthrough paper, Weiss and Choi reported that the neurotoxic potential of BMAA is greatly enhanced in the presence of physiological concentrations of bicarbonate ions.[34] They went on to show that, in presence of bicarbonate, BMAA acts on NMDA ionotropic glutamate receptors causing marked depolarization of the membrane potential.[35] Allen and coworkers later confirmed these findings, but reported that the effect can be blocked by antagonists of non-NMDA ionotropic glutamate receptors.[36]

Nedeljkov *et al.* investigated the effects of L-BMAA on Retzius nerve cells of isolated ganglia of the leech *Haemopis sanguisuga* and showed that the presence of bicarbonate ions produces a 4-fold increase in BMAA-induced depolarization of the membrane potential.[37] Lopicic and colleagues, using the same model, reported that application of both 1 mmol L^{-1} L-BMAA in Ringer solution containing 20 mmol L^{-1} bicarbonate caused a significant 74 % decrease in the input resistance of directly polarized membrane and that the non-NMDA receptor antagonist 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) at a concentration of

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100 μmol L^{-1} decreased the effect of L-BMAA on membrane potential by 57 %. The authors also presented evidence for a rise in the intracellular Na^+ concentration $(Na^+)_c$ and decrease in the intracellular K^+ concentration $(K^+)_c$ during BMAA induced depolarizations. The application of 2 mmol L^{-1} L-BMAA in bicarbonate Ringer for 4 min led to an average increase of $(Na^+)_c$ by 30.13±13.21 mmol L^{-1}, indicating a rapid influx of sodium into the cell, while the same concentration of L-BMAA produced a decrease of $(K^+)_c$ by 15.76±0.43 mmol L^{-1}, indicating a rapid efflux of K^+ from the cell.[38]

BMAA was also shown to produce a rise in the intracellular Ca^{2+} concentration,[39–41] and induce oxidative stress. Rao *et al.*[40] examined the effects of BMAA on reactive oxygen species (ROS) production in motor neurons from dissociated mouse spinal cord cultures using the oxidant-sensitive fluorophore, hydroethidine (HEt). The cells were loaded with HEt and imaged before and after 30 min exposure to BMAA (1–3 mM). The motor neurons showed significant increases in HEt oxidation several minutes after addition of BMAA and the BMAA-induced ROS generation was dose dependent.[40] Lobner and coworkers[41] investigated the mechanisms of BMAA toxicity on mixed cortical cell cultures containing neurons and astrocytes, prepared from fetal (15–16-day gestation) mice. Cellular oxidative stress was measured with the fluorescent dye dichlorofluorescein (DCF). Exposure to 3 mM BMAA for 3 h caused a significant increase in oxidative stress which was blocked by the free radical scavenger trolox.[41]

The presented evidence that BMAA acts *via* ionotropic glutamate receptors, increases the intracellular Na^+ and Ca^{2+} concentrations and induces oxidative stress all indicate that the amino acid might cause neurodegeneration through the mechanism of excitotoxicity.

Recently, Liu *et al.*[42] proposed that the mechanism of neurotoxicity of BMAA may be three-fold, involving not only direct action on the ionotropic glutamate receptors, but also activation of the metabotropic glutamate receptor 5 (mGluR5) and induction of oxidative stress unrelated to excitotoxicity. They found that BMAA inhibits the cystine/glutamate antiporter (system Xc−) mediated cystine uptake, which in turn leads to glutathione depletion and increased oxidetive stress. BMAA also appears to drive glutamate release *via* the system Xc− and this glutamate induces toxicity through activation of the mGluR5 receptor.[42]

Finally, the latest results by Nunn and Ponnusamy[4] provide evidence that several biochemical mechanisms are also involved in the neurotoxicity of BMAA. The authors showed that BMAA changes the distribution of taurine, glycine and serine between rat brain slices and their incubation medium. The glutamate/glutamine cycle between neurons and glia was also compromised as a result of BMAA administration. In model experiments, BMAA reacted non-enzymatically with pyridoxal-50-phosphate, releasing methylamine, and methylamine was also formed in rat liver and kidney homogenates when incubated with BMAA. The

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formation and release of methylamine is significant since chronic administration of methylamine to rats caused oxidative stress.[4]

4. BMAA AND THE ENVIRONMENT

The renewed interest in L-BMAA as an environmental neurotoxin stemmed from a series of papers by Cox *et al.*[4] They first established that the source of L--BMAA in *Cycas* palms are cyanobacteria of the genus *Nostoc* living as endosymbionts in the corraloid roots of the palm.[43] Axenic cultures of *Nostoc* isolated from corraloid roots of *C. micronesica* were found to produce 0.3 μg g^{-1} BMAA, while roots with flourishing cyanobacterial infections had 37 μg g^{-1} BMAA. Uninfected roots contained no BMAA.[43] Furthermore, Cox and coworkers presented evidence for biomagnification of BMAA through the Guamanian ecosystem; from cyanobacteria (0.3 μg g^{-1}) to *Cycad* seeds (up to 1161 μg g^{-1}), to bats *P. mariannus mariannus* (3556 μg g^{-1}), which are consumed as a delicacy in the diet of the people affected by ALS/PDC in Guam.[43]

However, the chemical nature of BMAA would make the molecule seem a poor candidate for bioaccumulation within an ecosystem since, unlike other biomagnified compounds, BMAA is not lipophilic and thus its accumulation in fatty tissues would seem unlikely. This issue was resolved by Murch and colleagues.[31] The group reported that BMAA occurs not only as a free amino acid, but can also be released from a bound form by acid hydrolysis. After first removing free amino acids from tissue samples of various trophic levels in Guam, Murch and coworkers hydrolyzed the remaining fraction and found BMAA concentrations to increase 10- to 240-fold. The authors comment that this protein-bound form of BMAA may function as an endogenous neurotoxic reservoir, accumulating and being transported between trophic levels and subsequently being released during digestion and protein metabolism.[31]

Finally, Cox *et al.* tested 11 *Nostoc* strains isolated from symbioses with lower and higher plants, and 30 laboratory strains of free-living cyanobacteria, covering all major taxonomic groups and found 8 out of 11 *Nostoc* strains, and 29 out of the 30 laboratory strains contained BMAA.[44]

The ubiquity of cyanobacteria in terrestrial, freshwater, brackish and marine environments, combined with the process of biomagnification, opened up an interesting possibility for widespread exposure to BMAA in concentrations sufficient for neurotoxicity. This started a worldwide search for the presence of BMAA in the environment.

Several methods have been reported to detect BMAA in cyanobacterial, plant and animal tissue samples, including high performance liquid chromategraphy (HPLC), gas chromatography–mass spectrometry (GC–MS), liquid chromatography–heated electrospray ionization–mass spectrometry/mass spectrometry

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(LC–ESI–MS/MS) and a method for underivatized BMAA using an amino acid analyzer.

Using three different high performance liquid chromatography (HPLC) techniques and two different liquid chromatography/mass spectrometry (LC/MS) techniques, Banack and coworkers demonstrated that the marine *cyanobacterial* species represented by *Nostoc* CCMED-001 produce β-*N*-methylamino-L-alanine. The concentration of BMAA in the specimens ranged from 7 to 25μg g^{-1}.[45]

Metclaf *et al.* analyzed 12 environmental samples, including blooms, scum and mats from waterbodies throughout the United Kingdom, collected over a 14--year period.[46] The waterbodies from which the samples were collected consisted of 11 inland freshwaters and one coastal brackish water. All of the waterbodies are of high, and often multiple usages – seven are abstracted for drinking water treatment, five are used as recreational waters, four as fisheries and one for livestock watering. BMAA was found to be present in all the examined samples in concentrations ranging from 8 to 287 μg g^{-1}. The authors also reported the occurrence of BMAA in waterbodies which are used for drinking water after treatment. Whether the processes of drinking water treatment remove or destroy BMAA requires investigation.

The use of cyanobacteria has also been reported in the Peruvian highlands.[47] The colonies of *Nostoc* commune (locally called llullucha) are harvested by indigenous peoples from high altitude vernal pools and lakes throughout the Peruvian Andes, and sold on the local markets. The colonies are used for food and medicine. As food, the colonies are preferred fresh, but can also be sun-dried to preserve them for the dry season. *Nostoc* commune is also used as a famine food, particularly when potatoes are scarce. Furthermore, llullucha is locally believed to be rich in calcium and is given to children as a milk substitute, and represents an ingredient of a local stew called picante.

Medicinally, *Nostoc* is used in the Peruvian highlands to treat fevers and inflammation; it is drunk after maceration. It is also applied topically by wrapping mashed *Nostoc* in a cloth around the waist overnight to treat stomach, liver, and kidney pain or taken internally after boiling for the same ailments. Large colonies are also macerated and applied topically to assist in the final stages of a difficult labor and delivery.

Johnson and coworkers tested 21 samples of Nostoc commune from seven local markets for the presence of BMAA and found it present in all the samples in concentrations ranging from 2.04 to 21.51 μg g^{-1}.[47]

Esterhuizen and Downing investigated for the presence of BMAA in cyanobacterial cultures representing taxonomic diversity and geographic distribution in southern Africa.[48] The cyanobacteria were collected from various freshwater impoundments that are used for agricultural and recreational activities, as well as from raw water sources for potable water production. All strains, except one,

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were reproducibly positive for BMAA, although several cultures were below the limit for quantification. Where BMAA could be quantified, it was found to be present in concentrations of 0.05–2755.6 μg g^{-1}. No correlation between the BMAA concentrations was observed within or between taxonomic groups or geographic locations. However, considerable difference in the BMAA content was found between extracts from different culture phases for the same strain, indicating that a number of factors, such as growth conditions, culture age and history, or nutritional or environmental stress, could influence the BMAA content in cyanobacteria.[49]

Li *et al.* have analyzed axenic cultures of *Microcystis aeruginosa* and Nostoc sp. at various growth stages, isolated from Chinese freshwaters, for BMAA. BMAA was detected in the Nostoc sp., but at very low concentrations (<0.07 pmol on column),[49] and BMAA was also detected in blue-green algae used for food supplements, freshwater fish and bottled water.[50]

Cox and coworkers report that cyanobacterial crusts and mats that are widespread in the deserts of Qatar contain BMAA.[51] These cyanobacterial crusts, which help bind the desert sands, are dormant throughout most of the year, but during brief spring rains actively photosynthesize. When disturbed by vehicular traffic or other activities, the dried crusts and mats can produce considerable amounts of dust, leading to significant exposure to BMAA and other cyanotoxins through inhalation. Since veterans of the 1990–1991 Gulf War younger than 45 years of age were reported to have an increased incidence of ALS compared to personnel who were not deployed, the authors went on to conclude that inhalation of BMAA, and other aerosolized cyanotoxins, may constitute a significant risk factor for the development of ALS and other neurodegenerative diseases.[51]

A cluster of ALS patients with incidence of the disease 10- to 25-times higher than expected, recorded in Enfield, New Hampshire, USA, was also linked to chronic exposure to BMAA and other cyanotoxins, since the town encompasses Lake Mascoma, which has a history of cyanobacteria algal blooms.[52] The authors suggested that possible routes of toxin exposure include inhalation of aerosolized toxins, consumption of fish, or ingestion of lake water.

BMAA-containing cyanobacteria were also found in drinking water sources and small pools within the Gobi Desert. Since such pools of water are crucial resources for wildlife inhabiting the area, the authors suggested assessment of cyanotoxin effects on organisms living in the Gobi Desert and other desert environments.[53]

Faassen and coworkers analyzed mixed species scum material from Dutch urban waters that suffer from cyanobacterial blooms. Free BMAA was detected at nine of the 21 sampled locations with a maximum concentration of 42 μg g^{-1}. Although the BMAA concentrations were relatively low, the authors concluded

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that co-occurrence with other cyanobacterial neurotoxins might pose a serious health risk.[54]

Avian vacuolar myelinopathy (AVM) is a neurological disease that produces uncoordinated behavior in affected birds. Feeding and sentinel trials, field surveys and genetic studies implicated the plant species *Hydrilla verticillata* (Hydrocharitaceae) and an associated epiphytic cyanobacterial species (order Stigonematales) as a causal link to AVM. Furthermore, Stigonematales were shown to produce BMAA. It was suggested that if biomagnification of BMAA occurs in these ecosystems, as was observed in the Guam ecosystem, then the consumption of fish and waterfowl from AVM-confirmed reservoirs could represent a significant human health risk.[55]

5. CONCLUSIONS

β-*N*-Methylamino-alanine is a neurotoxic amino acid produced by widespread cyanobacteria. A possible link between this amino acid and neurodegenerative diseases makes it a potential risk for animal and human health. Until more is known about the role of BMAA in progressive neurodegenerative illnesses, it is suggest that monitoring for the presence of BMAA in the environment would be prudent.

NOMENCLATURE

AD	Alzheimer's disease
ALS	Amyotrophic lateral sclerosis
ALS/PDC	Amyotrophic lateral sclerosis/Parkinsonism–dementia complex of the Western Pacific
AVM	Avian vacuolar myelinopathy
BMAA	β-*N*-Methylamino-alanine
CNQX	6-Cyano-7-nitroquinoxaline-2,3-dione
DCF	Dichlorofluorescein
GC–MS	Gas chromatography–mass spectrometry
HEt	Hydroethidine
HPLC	High performance liquid chromatography
$(K^+)_c$	Intracellular K^+ concentration
LC/MS	Liquid chromatography/mass spectrometry
LC–ESI–MS/MS	Liquid chromatography–heated electrospray ionization–mass spectrometry/mass spectrometry
$(Na^+)_c$	Intracellular Na^+ concentration
NMDA	*N*-Methyl-D-aspartate
ROS	Reactive oxygen species

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И З В О Д

ЕКСЦИТАТОРНА АМИНО КСЕЛИНА *β*-*N*-МЕТИЛАМИНО-L-АЛАНИН ЈЕ ПОТЕНЦИЈАЛНИ НЕУРОТОКСИН

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Аминокиселина *β*-L-метиламино-L-аланин (L-BMAA) повезана је са комплексом амиотрофичне латералне склерозе/паркинсонизам–деменције који се јавља у три одвојене етничке групе Западног Пацифика. Овај потенцијални неуротоксин производе цијанобактерије које живе у симбиози са кореном палми из рода *Cycas*. Првобитно је владало мишљење да L-BMAA представља ризик само за наведене западнопацифичке популације које у исхрани и лечењу користе велике количине семена палме *Cycas*. Новија истраживања, међутим, показују да цијанобактерије присутне у разнородним екосистемима у земљишту, сланим и слатким водама широм света такође производе ову аминокиселину. Имајући у виду потенцијални ризик који L-BMAA представља за здравље људи, било би важно пратити ниво ове аминокиселине у водама у којима су присутне цијанобактерије.

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