Available online at www.sciencedirect.com
ScienceDirect
Neurochemistry International 50 (2007) 998–1003
NEUROCHEMISTRY International
www.elsevier.com/locate/neuint

Invited review

Is there a role for naturally occurring cyanobacterial toxins in neurodegeneration? The beta-*N*-methylamino-L-alanine (BMAA) paradigm

Spiridon Papapetropoulos *

Department of Neurology, University of Miami, Miller School of Medicine, Room 4004, 1501 NW 9th Avenue, Miami, FL 33136, USA

Received 7 November 2006; received in revised form 6 December 2006; accepted 14 December 2006
Available online 14 January 2007

Abstract

The naturally occurring, non-essential amino acid beta-*N*-methylamino-L-alanine (BMAA) has been recently found in high concentrations in brain tissues of patients with tauopathies such as the Amyotrophic Lateral Sclerosis-Parkinsonism-Dementia Complex (ALS/PDC) in the South Pacific island of Guam and in a small number of Caucasian, North American patients with sporadic Alzheimer's disease. BMAA is produced by cyanobacteria that are present in all conceivable aquatic and/or terrestrial ecosystems and may be accumulated in living tissues in free and protein-bound forms through the process of biomagnification. Although its role in human degenerative disease is highly debated, there is mounting evidence in support of the neurotoxic properties of BMAA that may be mediated via mechanisms involving among others the regulation of glutamate. Glutamate-related excitotoxicity is among the most prominent factors in the etiopathogenesis of human neurodegenerative diseases. Due to the wide geographical distribution of cyanobacteria and the possible implications of BMAA neurotoxic properties in public health more research towards this direction is warranted.
© 2007 Elsevier Ltd. All rights reserved.

Keywords: BMAA; ALS/PDC; Tauopathies; Neurodegeneration; Neurotoxicity; Cyanobacteria; Neurotoxins

1. Introduction

There has been longstanding controversy about the relative importance of genetic versus environmental factors in neurodegeneration. In general, not only they are not mutually exclusive, but appear to be complementary. Apart from some rare monogenic forms of neurodegenerative diseases caused by mutations transmitted with a Mendelian pattern of inheritance such as the alpha-synuclein mutations in Parkinson's disease (PD) (Polymeropoulos et al., 1997), the presenilin mutations in Alzheimer's disease (AD) (Rogaev et al., 1995), and the superoxide dismutase mutations in ALS (Rosen et al., 1993) the majority of cases appear to have a multifactorial etiology where genetic susceptibility may confer selective vulnerability to environmental risk factors (Papapetropoulos and Mash, 2005). Naturally occurring plant components with toxic potential have been identified as risk factors for a wide array of neurological disorders (Spencer et al., 1993). Cycad toxins (Spencer et al., 1993), mycotoxins (fungal metabolites such as orchatoxin-A) (Sava et al., 2006), and botanical chemicals (i.e. rotenone) (Trojanowski, 2003) (among others) have been tightly linked to neurodegenerative human and animal disease.

Using the cluster approach (grouping of cases of a particular disorder in space and time) one may yield epidemiologically useful information that can be applied towards the determination of possible causes of neurodegeneration. This is the case of the Amyotrophic Lateral Sclerosis-Parkinsonism-Dementia Complex (ALS/PDC) of the western Pacific. Three foci of ALS/PDC have been identified in Guam, in Japan, and in western New Guinea (Armon, 2003). The best studied cluster, ALS/PDC of Guam was described in the middle of the last century and is characterized by either, a progressive dementing disorder with extrapyramidal, parkinsonian type of motor involvement or a progressive motor neuron syndrome similar to ALS. Less frequently both phenotypes coincide (Hirano et al., 1961). Neuropathology in all forms of ALS/PDC reveals a

* Tel.: +1 305 243 8461; fax: +1 305 243 3649.
E-mail address: spapapetropoulos@med.miami.edu (S. Papapetropoulos).

0197-0186/$ – see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.neuint.2006.12.011

tauopathy with cortical atrophy, neuronal loss and numerous neurofibrillary tangles (NFTs) widely distributed throughout the central nervous system. NFTs in ALS/PDC are similar both biochemically and immunohistochemically to the ones observed in AD. However, NFT localization that has striking similarities to a rarer tauopathy—progressive supranuclear palsy (PSP) (Hirano, 1992; Trojanowski et al., 2002). In addition, typical Lewy Body (LB) alpha-synuclein positive pathology-mostly seen in PD – has been identified – in the substantia nigra (Hirano et al., 1966) and the amygdala of Guamanian PDC patients (Forman et al., 2002; Yamazaki et al., 2000).

Apart from the familiar clustering of some ALS/PDC cases that points towards a genetic etiology (Steele, 2005), the major hypotheses associated with the ALS/PDC are undoubtedly environmental: several theories have postulated toxicity either caused by ingestion of environmental neurotoxins such as the ones found in cycad-based foods, an unknown slow viral agent (Maurizi, 1987), and an imbalance in water mineral content causing a parathyroid disorder that affects calcium, magnesium, and aluminium metabolism (Reed and Brody, 1975). The latter two appear to have been ruled out.

The implication – that there is a temporary exposure to an environmental risk factor, unique or concentrated in the Guamanian ecosystem, involved in the etiopathogenesis of ALS/PDC – has fueled decades of research and speculation. Several recent reports on the role of the naturally occurring non-essential amino acid beta-*N*-methylamino-L-alanine (BMAA) (Cox et al., 2003; Murch et al., 2004a,b), produced by certain cyanobacterial species, have refueled the controversy surrounding the pathogenesis of ALS/PDC. Based on pilot studies of the association of BMAA and sporadic tauopathies (i.e. Alzheimer's disease) the possible role of BMAA in at least some of these cases has been suggested (Murch et al., 2004a,b). In this review several issues surrounding BMAA and its possible relation to ALS/PDC and neurodegeneration are discussed.

2. BMAA and ALS/PDC in the island of Guam

Epidemiological studies have long indicated that consumption of a traditional Chamorro diet is the only variable significantly associated with ALS/PDC incidence in the island of Guam (Reed et al., 1987). Dietary habits analysis have identified the consumption of products of the seeds of cycad plants (i.e. cycad flour), as a likely cause of ALS/PDC (Whiting, 1963). The most immediately active toxin of cycad plants is cycasin, a glycoside component with hepatotoxic and carcinogenic effects, but only minimal neurotoxic effects. However, cycasin is usually removed by the extensive soaking process used to prepare cycad for consumption. Genetic risk may also be important because cases cluster among families to an extent, but do not follow an obvious pattern of inheritance (Reed et al., 1975).

After an observation that there might be parallels between the neurotoxicity of beta-*N*-oxalylamino-L-alanine (BOAA), the compound responsible for lathyrism (a form of motor neuron disease induced by excessive consumption of chickling peas) (Spencer et al., 1986a,b), and BMAA, which is present in the cycad, Spencer et al. (1986a,b) first proposed its involvement in the etiopathogenesis of ALS/PDC by producing an illness in monkeys with features of ALS and parkinsonism (Spencer et al., 1986a,b). Administration of BMAA in primates produced an acute/subacute toxicity model rather than simulating the known long latency associated with the development of ALS/PDC (Spencer et al., 1987). Furthermore, in these early studies, the concentration of BMAA in processed cycad flour was reported too low (early studies did not measure the bound fraction of BMAA and only reported on the free) to produce comparable disease states in humans (Duncan et al., 1990; Kisby et al., 1992). Although a possible link between acute neurotoxicity/neurodegeneration and BMAA was first established at that time, apparent lack of solid evidence for adequate exposure through consumption of cycad flour prevented further research into the matter. Doses fed to produce disease in monkeys were estimated to be equivalent to impractical levels of human ingestion equivalent to 1500 kg of processed cycad flour over a 12-week period. However, these levels were acquired using standard extraction methods based on a soluble fraction obtained by using trichloroacetic acid (TCA) following tissue maceration. It now emerges that there is a previously non-described, and significantly enriched fraction of BMAA that is associated in an uncharacterized way with the protein component of plant and animal tissues (Murch et al., 2004a,b). However, when the insoluble, protein-containing fraction following TCA extraction is further hydrolysed to release BMAA from protein, there is a further pool of ''protein bound'' BMAA that is present in a ratio of between 60:1 and 120:1 compared with the pool of ''free BMAA''. These observations extend to cycad flour obtained on Guam following the normal water-based detoxification process, which also contains a significant pool (approximately 60–80 mg/g BMAA) of ''bound'' BMAA (Ince and Codd, 2005). Therefore, the low concentrations previously reported may not have been accurate predictors of exposure to BMAA and the development of ALS/PDC.

Cycad seeds have been continuously used by the Chamorros as a source of tortilla flour (Banack and Cox, 2003). However, the incidence of new ALS cases among the Chamorros is constantly decreasing ($50{:}10^5$ for 1945–1959 to $7.5{:}10^5$ for 1980–1989) (Galasko et al., 2002). The rapid and dramatic decline in the incidence of ALS over a period of fewer than 50 years is easiest to reconcile with an environmental factor that contributed to the disease in the past but operates much less strongly, if at all, at present. Such an environmental factor was first presented by Cox and Sacks (2002) who related exposure to very high concentrations of BMAA, with consumption of flying foxes (a prized food item of the indigenous Chamorro people who boil them in coconut cream and eat them whole) that feed on cycads. They reported that BMAA is biomagnified (increasing accumulation of bioactive, often deleterious molecules through successively higher trophic levels of a food chain) in the Guam ecosystem (Cox et al., 2003). BMAA is produced by cyanobacteria that can be found in almost every conceivable habitat, from oceans to

Download English Version:

https://daneshyari.com/en/article/2202028

Download Persian Version:

https://daneshyari.com/article/2202028

Daneshyari.com