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50 years of research on α-amino-β-methylaminopropionic acid (β-methylaminoalanine)

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ABSTRACT

The isolation of α-amino-β-methylaminopropionic acid from seeds of *Cycas circinalis* (now *C. micronesica* Hill) resulted from a purposeful attempt to establish the cause of the profound neurological disease, amyotrophic lateral sclerosis/parkinsonism/dementia, that existed in high frequency amongst the inhabitants of the western Pacific island of Guam (Guam ALS/PD). In the 50 years since its discovery the amino acid has been a stimulus, and sometimes a subject of mockery, for generations of scientists in a remarkably diverse range of subject areas. The number of citations of the original paper has risen in the five decades from a few to 120 within the decade 2007–2016 and continues at a high rate into the next decade. The reasons for this remarkable outcome are discussed and examples from the literature are used to illustrate the wide range of scientific interest that the original paper generated.

1. Introduction

The isolation of α-amino-β-methylaminopropionic acid (MeDAP; later termed β-methylaminoalanine, BMAA) was first announced in the pages of *Phytochemistry* (Vega and Bell, 1967); this account has been written to commemorate the 50th anniversary of that event. The paper was followed shortly afterwards (also in *Phytochemistry*) by details of the stereochemistry, chemical synthesis and neurotoxicity of the compound (Vega et al., 1968) (see Figs. 1 and 3).

Although this was the first discovery of the amino acid in nature, it had been synthesised some twenty years earlier (Eiger and Greenstein, 1948), but no further investigations occurred subsequently. Thus was established the reputation of this amino acid for being alternatively in or out of fashion (Fig. 2 shows the frequency of citations per decade since 1967). The structure is shown in Fig. 1.

2. A brief history and the decade 1967–1976 (8 citations)

The isolation of α-amino-β-methylaminopropionic acid (remarkably achieved by Armando Vega from only a small amount of seed material) was a purposeful attempt to find a neurotoxic substance in cycad seeds, which were used historically as a foodstuff by the indigenous Chamorro population of Guam, an island in the Western Pacific. Photographs of a specimen of *Cycas circinalis*, its seeds and leaf are shown in Fig. 3.

In the past, Chamorros had suffered from a high frequency of the profound neurological disease amyotrophic lateral sclerosis/parkinsonism/dementia (Guam ALS/PD). An understanding of the causes of the Guamanian disorder was thought likely to provide clues to the aetiology of sporadic amyotrophic lateral sclerosis (motor neuron disease), Parkinson's disease and Alzheimer's dementia in Western societies. Accounts of the history of this period will be found in Arnold et al. (1953); Kurland and Mulder, 1954; Whiting, 1963. In brief: Marjorie Whiting, who was working in the field in Guam studying the dietary habits of Chamorros, read a paper by Arthur Bell (1964) concerning the neurotoxicity of β-ODAP, an amino acid isolated from *Lathyrus sativus* seed (Rao et al.,

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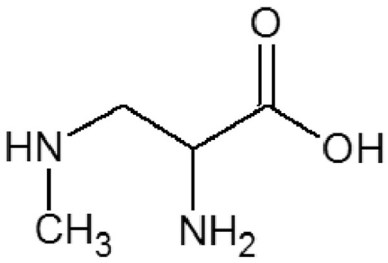

Fig. 1. Structure of α-amino-β-methylaminopropionic acid (MeDAP); β-methylaminoalanine (BMAA). The amino acid is usually isolated as the monohydrochloride salt but, *in vivo* at physiological values of pH, the molecule is neutral. The negative charge on the carboxyl group is balanced by partial positive charges on the 2-amino and 3-methylamino groups (see Nunn, 2009). The 2-amino group is virtually uncharged at physiological pH values (Fig. 6).

1964). This compound was thought to be causative of neurolathyrism, a chronic neurological disease seen in subjects of the Indian sub-continent and Ethiopia, who consumed the seed as a staple in times of famine. On paper electrophoresis at pH 3.6, β-ODAP moved as a strongly acidic amino acid; Bell's analysis by this method of an aqueous ethanolic extract of the endosperm of a cycad seed (believed to be *Cycas circinalis*, but now classified as *Cycas micronesica* Hill) sent to him in London from Guam by Whiting, revealed instead an amino acid with basic characteristics. It was this compound that Vega, using ion-exchange chromatography, isolated so expertly, and which became known, in laboratory parlance, as 'Armando's compound'. The new amino acid was quickly shown to be neurotoxic to experimental animals, but the initial choice of day-old-chicks was unusual. However, Rao et al. (1964) had shown that the *Lathyrus sativus* neurotoxin, β-ODAP, caused neurotoxic signs when administered intraperitoneally to such birds; the present author argued that, were the new amino acid also a neurotoxin, a similar response might be expected from this bioassay. Comparing Rao's data, it was evident that the two amino acids were both neurotoxic to day-old chicks over a similar dosage range. The cycad amino acid was also neurotoxic to mice and rats, while β-ODAP was not, a dichotomy that was not resolved until later (Vardhan et al., 1997). Photographs of those involved in this early phase of the cycad story are shown in Fig. 4.

The potential neurotoxicity of cycads had been under investigation for some years following medical observations on Guam following the Second World War and a series of six conferences was held under the auspices of the National Institutes of Health, Bethesda, Maryland, from 1962 to 1971, in which cycasin (methylazoxymethanol β-D-glucoside) and similar compounds containing different glycosyl groups, held centre stage. These substances were shown to be carcinogenic and cycasin was a component of cycad seeds (Marsumoto and Strong, 1963). It might be thought that, in these circumstances, the announcement of a neurotoxic compound from cycad seeds would have stimulated the scientific and medical community, but the response to a paper presented at the Fifth Conference (Bell et al., 1967), was one of disinterest and mild criticism. Neuropathologists in the United Kingdom expressed no interest, an attempt to construct a chronic model with neurological signs in rats was unsuccessful (Polsky et al., 1972) and no neuropathological indicators appeared in neonatal rats treated subcutaneously with the amino acid (P.B. Nunn and G. L. Laqueur, 1970; unpublished data; but see Karlsson et al., 2009).

An interesting addition to the chemistry of the cycad amino acid was that the component later named the 'soluble-bound fraction' (Faassen et al., 2016) occurred not only in extracts of *Cycas micronesica* seed (Polsky et al., 1972), but also in the seed of all cycad species that were examined (Dossaji and Bell, 1973). (The chemical nature of BMAA in this fraction remains unknown, but it may be a γ-glutamyl peptide (Kasai and Larsen, 1980), a water-soluble peptide such as galantine 1 (Fig. 5), or a siderophore of the type known to be synthesised from other diaminomonocarboxylic acids by some bacteria (see Nunn and Codd, 2017, Fig. 7).

Within the same decade as the original discovery, the cycad amino acid was also found to exist in a bacterial peptide, along with its probable metabolic precursor 2,3-diaminopropanoic acid, in galantine 1 (Fig. 5), produced by *Bacillus* (now *Paenibacillus*) *pulvifaciens* (Shoji et al., 1975; see Sakai and Ohfune, 1990). This was the first bound form of the amino acid to be identified and the first time that the cycad amino acid was detected outside of the *Cycadales*.

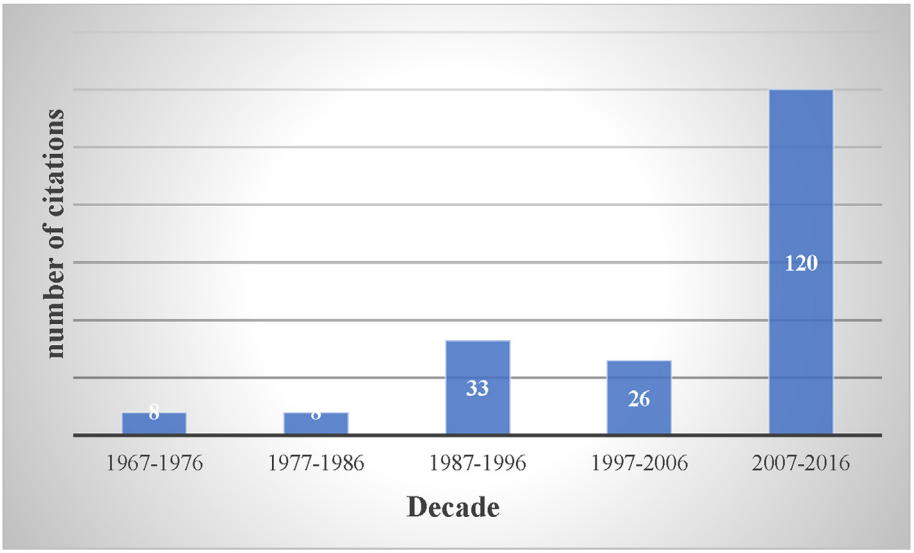

Fig. 2. Number of citations per decade of Vega, A., Bell, E.A., 1967. α-Amino-β-methylaminopropionic acid, a new amino acid from seeds of *Cycas circinalis*. Phytochemistry 6, 759–762. The data (from Google Scholar) are given for each of five 10-year intervals from 1967 to 2016.