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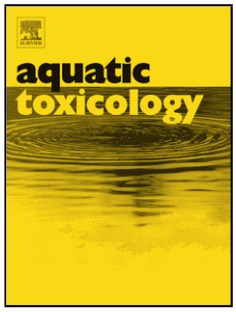

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PII: S0166-445X(18)30318-7
DOI: https://doi.org/doi:10.1016/j.aquatox.2018.03.036
Reference: AQTOX 4908

To appear in: *Aquatic Toxicology*

Received date: 24-11-2017
Revised date: 29-3-2018
Accepted date: 30-3-2018

Please cite this article as: S. Spasic, M. Stanojevic, J. Nesovic Ostojic, S. Kovacevic, M. Prostran, S. Lopicic, Extensive depolarization and lack of recovery of leech Retzius neurons caused by 2,4 diaminobutyric acid, *<![CDATA[Aquatic Toxicology]]>* (2018), https://doi.org/10.1016/j.aquatox.2018.03.036

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ACCEPTED MANUSCRIPT

Extensive depolarization and lack of recovery of leech Retzius neurons caused by 2,4 diaminobutyric acid

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Abstract

In this paper we present, for the first time, a detailed account of electrophysiological effects of 2,4-diaminobutyric acid (2,4-DABA). 2,4-DABA is a neurotoxic non-protein amino acid produced by *Cyanobacteria* with a possible link to neurodegenerative disorders in animals and humans. Intracellular recordings were performed on Retzius nerve cells of the leech *Haemopis sanquisuga* using glass microelectrodes filled with 3 mol/L KCl . Our results show that 2,4-DABA is an excitatory amino acid, causing membrane depolarization in a concentration-dependent manner. The most prominent depolarizations of 39.63 ± 2.22 mV and 47.05 ± 4.33 mV, induced by $5 \cdot 10^{-3}$ and 10^{-2} mol/L 2,4-DABA respectively, are several times larger than maximal depolarizations induced by either Glutamate, Aspartate, β-N-methylamino-alanine (BMAA) or β-N-oxalylamino-alanine (BOAA) on our model. These 2,4-DABA induced depolarizations evolve through two distinct stages, which is a novel phenomenon in electrical cell activity upon application of an excitatory amino acid, at least on our model. Involvement of two separate mechanisms, suggested by the two stage phenomenon, is discussed in the paper. We also provide evidence that 2,4-DABA induces irreversible functional disturbances in neurons in a concentration-dependent manner, since only half of the cells recovered normal electrical activity after application of $5 \cdot 10^{-3}$ mol/L 2,4-DABA, and none recovered after application of 10^{-2} mol/L 2,4-DABA. Effects of both L-2,4-DABA and DL-2,4-DABA were tested and are not significantly different.

Keywords: 2,4 diaminobutyric acid, membrane potential, neurotoxicity, Cyanobacteria, leech

1. Introduction

2,4-diaminobutyric acid (2,4-DABA) is a non-protein amino acid first identified by Catch as a metabolic product of bacteria (Catch et al., 1948). The first report of the neurotoxic properties of 2,4-DABA followed soon (Riggs et al., 1954). In this paper Riggs and associates have applied 2,4-DABA to rats in a dose of 7 mmol/L/kg subcutaneously, which resulted in preconvulsive and convulsive behavior and death. Chronic exposure to 2 mmol/L/kg for 7 days led to little change in behavior, but produced focal morphological degenerative changes most pronounced in the Purkinje cells of the cerebellum. Riggs et al. have concluded that 2,4-DABA has a strong neurotoxic action on rats (Riggs et al., 1954).

These findings have been subsequently confirmed, and additional neurotoxic manifestations, including hyperirritability, weakness in hind legs and tremors in the upper extremities, were observed in rats (Chen et al., 1972; O'Neal et al., 1968) and mice (Ronquist et al., 1980). Aside from being neurotoxic, 2,4-DABA has been shown to be hepatotoxic (O'Neal et al., 1968), and to induce irreversible damage to fibrosarcoma (Ronquist et al., 1980), glioma (Ronquist et al., 1984), and hepatoma (Blind et al., 2003) cells. However, 2,4-DABA has seldom appeared in literature in context of its toxicity, until it was found to be present together with β-N-methylamino-L-alanine (BMAA) in cyanobacterial samples.

BMAA is a neurotoxic amino acid associated with Western Pacific amyotrophic lateral sclerosis Parkinsonism /dementia complex. Ever since Cox et al. (2003) proposed that *Cyanobacteria* produce BMAA, there has been a continuous effort to detect and quantify BMAA in various matrices. Although the field has been plagued with controversy, the presence of BMAA in aquatic ecosystems is accepted (Faassen, 2014), and BMAA is reported to occur in different geographical locations and environments (Merel et al., 2013).

In many studies searching for BMAA, from the earliest reports (Banack and Cox, 2003) to the most recent ones (Chatziefthimiou et al., 2017), 2,4-DABA was detected together with BMAA, and often attributed a relevant and significant role in environmental toxicity. For instance, analysis of feathers from the carcasses of Lesser Flamingos, during mass mortality events, showed the presence

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