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Damaging effects of the cyanotoxin BMAA in cultured retinal cells: neuroprotection by Serine and retinoid X receptor (RXR) activation

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Abstract

Purpose : The chronic intake of the non-proteic aminoacid BMAA, a toxin released by cyanobacteria present in most dams and water resources, has been linked to the development of neurodegenerative diseases. We demonstrated that BMAA promotes cell death in cultured amacrine and photoreceptor neurons (PHRs), and Müller glial cells (MGCs) cannot prevent this degeneration. We here investigated whether serine and RXR activation can prevent BMAA-induced death, and whether MGCs are affected by BMAA.

Methods : We used purified neuronal and glial cultures, obtained from newborn rat retinas (PN2 and PN3-5, respectively). We pre-treated neuronal cultures with 25 µM serine or 1 µM HX630, a RXR agonist, before incubation with 0.4 µM BMAA for 3 days. MGC cultures were treated with BMAA (0.4, 1 and 10 µM) added either at day 1 or, successively, at days 1 and 4, and incubated for either 3 or 9 days (short and long-term BMAA exposure, respectively). We evaluated cell death and apoptosis by Trypan Blue, TUNEL assay, and DAPI staining; mitochondrial activity by Mitotracker and MTT assays; and ROS levels with the DCDCDHF probe. Results represent the average of at least three experiments (n≥3). For statistical analysis we used ANOVA followed by Tukey's test.

Results : In pure neuronal cultures serine and HX630 pre-treatment prevented BMAA-induced increase in fragmented nuclei ($p \leq 0.001$; $p \leq 0.01$) and apoptosis ($p \leq 0.01$) in PHRs, while in amacrine neurons they blocked the increase in fragmented nuclei ($p \leq 0.001$), but only serine prevented apoptosis ($p \leq 0.01$). In both neuronal types, HX630 diminished ROS levels ($p \leq 0.001$) and improved mitochondrial activity ($p \leq 0.001$), which were affected by BMAA. In contrast, MGCs showed nuclear alterations ($p \leq 0.05$) after long-term exposure to BMAA but preserved their viability ($p \leq 0.01$). Additionally, 1 and 10 µM BMAA increased their cellular metabolic activity after a short-term, but not after a long-term BMAA exposure ($p \leq 0.01$).

Conclusions : These results suggest that BMAA induces subcellular changes in both neurons and MGCs, affecting viability in neurons but not in MGCs. Noteworthy, RXR activation and serine supplementation protect retinal neurons from BMAA toxicity. These results might contribute to develop new therapeutic strategies for retinopathies often associated with chronic BMAA exposure.

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