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Neuroprotection against N-Methyl-D-Aspartate-Induced Optic Nerve and Retinal Degeneration Changes by Philanthotoxin-343 to Alleviate Visual Impairments Involve Reduced Nitrosative Stress

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Abstract : Glaucoma is the global leading cause of irreversible blindness. Currently, the available treatment strategy only involves lowering intraocular pressure (IOP); however, the condition often progresses despite lowered or normal IOP in some patients. N-methyl-D-aspartate receptor (NMDAR) excitotoxicity often occurs in neurodegeneration-related glaucoma; thus it is a relevant target to develop a therapy based on neuroprotection approach. This study investigated the effects of Philanthotoxin-343 (PhTX-343), an NMDAR antagonist, on the neuroprotection of NMDA-induced glaucoma to alleviate visual impairments. Male Sprague-Dawley rats were equally divided: Groups 1 (control) and 2 (glaucoma) were intravitreally injected with phosphate buffer saline (PBS) and NMDA (160nM), respectively, while group 3 was pre-treated with PhTX-343 (160nM) 24 hours prior to NMDA injection. Seven days post-treatments, rats were subjected to visual behavior assessments and subsequently euthanized to harvest their retina and optic nerve tissues for histological analysis and determination of nitrosative stress level using 3-nitrotyrosine ELISA. Visual behavior assessments via open field, object, and color recognition tests demonstrated poor visual performance in glaucoma rats indicated by high exploratory behavior. PhTX-343 pre-treatment appeared to preserve visual abilities as all test results were significantly improved ($p < 0.05$). H&E staining of the retina showed a marked reduction of ganglion cell layer thickness in the glaucoma group; in contrast, PhTX-343 significantly increased the number by 1.28-folds ($p < 0.05$). PhTX-343 also increased the number of cell nuclei/100µm2 within inner retina by 1.82-folds compared to the glaucoma group ($p < 0.05$). Toluidine blue staining of optic nerve tissues showed that PhTX-343 reduced the degeneration changes compared to the glaucoma group which exhibited vacuolation overall sections. PhTX-343 also decreased retinal 3- nitrotyrosine concentration by 1.74-folds compared to the glaucoma group ($p < 0.05$). All results in PhTX-343 group were comparable to control ($p > 0.05$). We conclude that PhTX-343 protects against NMDA-induced changes and visual impairments in the rat model by reducing nitrosative stress levels.

Keywords : excitotoxicity, glaucoma, nitrosative stress , NMDA receptor , N-methyl-D-aspartate , philanthotoxin, visual behaviour
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