The Retinoprotective Effects and Mechanisms of Fungal Ingredient 3,4-Dihydroxybenzalacetone through Inhibition of Retinal Müller and Microglial Activation

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Abstract : Retina glial activation and neuroinflammation have been confirmed to cause devastating responses in retinodegenerative diseases. The expression and activation of matrix metalloproteinase (MMP)-9 and inducible nitric oxide synthase (iNOS) could be exerted as the crucial pathological factors in glaucoma- and blue light-induced retinal injuries. The present study aimed to investigate the retinoprotective effects and mechanisms of fungal ingredient 3,4dihydroxybenzalacetone (DBL) isolated from Phellinus linteus in the retinal glial activation and retinodegenerative animal models. According to the cellular studies, DBL significantly and concentration-dependently abrogated MMP-9 activation and expression in TNF α -stimulated retinal Müller (rMC-1) cells. We found the inhibitory activities of DBL were strongly through the STAT- and ERK-dependent pathways. Furthermore, DBL dramatically attenuated MMP-9 activation in the stimulated Müller cells exposed to conditioned media from LPS-stimulated microglia BV-2 cells. On the other hand, DBL strongly suppressed LPSinduced production of NO and ROS and expression of iNOS in microglia BV-2 cells. Consistently, the phosphorylation of STAT was substantially blocked by DBL in LPS-stimulated microglia BV-2 cells. In the evaluation of retinoprotective functions, the high IOP-induced scotopic electroretinographic (ERG) deficit and blue light-induced abnormal pupillary light response (PLR) were assessed. The deficit scotopic ERG responses markedly recovered by DBL in a rat model of glaucoma-like ischemia/reperfusion (I/R)-injury. DBL also reduced the aqueous gelatinolytic activity and retinal MMP-9 expression in high IOP-injured conditions. Additionally, DBL could restore the abnormal PLR and reduce retinal MMP-9 activation. In summary, DBL could ameliorate retinal neuroinflammation and MMP-9 activation by predominantly inhibiting STAT3 activation in the retinal Müller cells and microglia, which exhibits therapeutic potential for glaucoma and other retinal degenerative diseases. Keywords : glaucoma, blue light, DBL, retinal Müller cell, MMP-9, STAT, Microglia, iNOS, ERG, PLR

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