Protective effects of apolipoprotein E-containing lipoproteins against glaucomatous optic neuropathy

Hideki Hayashi, Mariko Yamada, Misuzu Mori, Mio Kobayashi, Hikaru Koide, Takuya Kojima, Chihaya Mukaigaito, Bo Yuan, Norio Takagi

Applied Biochemistry, Tokyo University of Pharmacy and Life Sciences, Japan

Lipoproteins secreted from glia have important roles of lipid metabolism and transport in the central nervous system. Apolipoprotein (apo) E is a major apo in the central nervous system. It has been reported that apo E-containing lipoproteins not only transport lipids from glia to neurons but also stimulate synaptogenesis in central nervous system neurons. We have also reported that glia-derived apo E-containing lipoproteins promote axon extension of retinal ganglion cells and protect them from neurodegeneration induced by trophic factor-withdrawal and glutamate excitotoxicity via low density lipoprotein receptor-related protein 1 (LRP1). It has been shown that alpha 2-macroglobulin (a2M), which acts as an LRP1 ligand, is elevated in aqueous humor of patients with glaucoma. Here, we showed that administration of apo E-containing lipoproteins attenuated retinal degeneration led by intravitreal injection of N-methyl-D-aspartate in rats, a model of glaucoma. The apo E-containing lipoproteins also decreased the elevated a2M level in aqueous humor of the glaucoma model. The neuroprotective effect of apo E-containing lipoproteins against excitotoxicity in primary cultured retinal ganglion cells was interfered by a2M, but an exogenous administration of the lipoproteins overcame the interference. Furthermore, addition of apo E-containing lipoproteins into the medium of primary cultured retinal glia decreased mRNA and protein levels of a2M in a receptor-mediated manner. These findings indicate a potential therapeutic approach of apo E-containing lipoproteins or LRP1 agonists by decreasing the a2M level in the retina as treatments for neurodegenerative disorders such as glaucoma.