GluA2 Trafficking Is Involved in Apoptosis of Retinal Ganglion Cells Induced by Activation of EphB/EphrinB Reverse Signaling in a Rat Chronic Ocular Hypertension Model

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EphB1, expressed in Müller cells, and ephrinB2, expressed in both Müller cells and retinal ganglion cells (RGCs) , constitute an EphB/ephrinB reverse signaling in RGCs. Whether and how this reverse signaling is involved in RGC apoptosis in a rat chronic ocular hypertension (COH) model was investigated. In the COH model, both EphB1 and ephrinB2 were significantly increased and the reverse signaling was activated, which was accompanied by increased protein levels of phosphorylated (p) src, GluA2, and p-GluA2. Intravitreal injection of EphB2-Fc, an activator of ephrinB2, induced an increase in TUNEL-positive signals in normal retinae. A coimmunoprecipitation assay demonstrated direct interactions among ephrinB2, p-src, and GluA2.

Moreover, in COH rats the expression of GluA2 proteins on the surface of retinal cells was decreased. Such GluA2 endocytosis could be prevented by preoperational intravitreal injection of 4-amino-3-(4-chlorophenyl) -1-(t-butyl) -1H-pyrazolo [3,4-d] pyrimidine (PP2) , an inhibitor of src family tyrosine kinases, and possibly involved the protein interacting with C kinase 1 and phosphorylation of GluA2. In normal rats, intravitreal injection of EphB2-Fc caused changes in these protein levels similar to those observed in COH rats, which all could be avoided by preinjection of PP2. Patch-clamp experiments further showed that the current-voltage relationship of AMPA receptor-mediated EPSCs of RGCs exhibited stronger inward rectification in EphB2-Fc-injected rats.

Furthermore, preinjection of PP2 or N-[3-[[4-[(3-aminopropyl) amino]butyl]amino]propyl]-1-naphthaleneacetamide trihydrochloride) (Naspm) , a Ca(2+) -permeable GluA2-lacking AMPA receptor inhibitor, remarkably inhibited RGC apoptosis in either EphB2-Fc-injected or COH rats. Together, elevated GluA2 trafficking induced by activated EphB2/ephrinB2 reverse signaling likely contributes to RGC apoptosis in COH rats.

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