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Inhibition of Glutamate Carboxypeptidase Activity Protects Retinal Ganglionic Cell Death Induced by Ischemia-Reperfusion by Reducing the Astroglial Activation in Rat

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Abstract : Excessive activation of glutamate receptor is thought to be involved in retinal ganglion cell (RGC) death after ischemia- reperfusion damage. Glutamate carboxypeptidase II (GCPII) is an enzyme responsible for the synthesis of glutamate. Several studies showed that inhibition of GCPII prevents or reduces cellular damage in brain diseases. Thus, in this study, we examined the expression of GCPII in rat retina and the role of GCPII in acute high IOP ischemia-reperfusion damage of eye by using a GCPII inhibitor, 2-(phosphonomethyl) pentanedioic acid (2-PMPA). Animal model of ischemia-reperfusion was induced by raising the intraocular pressure for 60 min and followed by reperfusion for 3 days. Rats were randomly divided into four groups: either intra-vitreous injection of 2-PMPA (11 or 110 ng per eye) or PBS after ischemia-reperfusion, 2-PMPA treatment without ischemia-reperfusion and sham-operated normal control. GCPII immunoreactivity in normal rat retina was detected weakly in retinal nerve fiber layer (RNFL) and retinal ganglionic cell layer (RGL) and also inner plexiform layer (IPL) and outer plexiform layer (OPL) strongly where are co-stained with an anti-GFAP antibody, suggesting that GCPII is expressed mostly in Muller and astrocytes. Immunostaining with anti-BRN antibody showed that ischemia- reperfusion caused RGC death (31.5 %) and decreased retinal thickness in all layers of damaged retina, but the treatment of 2-PMPA twice at 0 and 48 hour after reperfusion blocked these retinal damages. GCPII level in RNFL layer was enhanced after ischemia-reperfusion but was blocked by PMPA treatment. This result was confirmed by western blot analysis showing that the level of GCPII protein after ischemia- reperfusion increased by 2.2- fold compared to control, but this increase was blocked almost completely by 110 ng PMPA treatment. Interestingly, GFAP immunoreactivity in the retina after ischemia- reperfusion followed by treatment with PMPA showed similar pattern to GCPII, increase after ischemia-reperfusion but reduction to the normal level by PMPA treatment. Our data demonstrate that increase of GCPII protein level after ischemia-reperfusion injury is likely to cause glial activation and/or retinal cell death which are mediated by glutamate, and GCPII inhibitors may be useful in treatment of retinal disorders in which glutamate excitotoxicity is pathogenic.

Keywords : glutamate carboxypepptidase II, glutamate excitotoxicity, ischemia-reperfusion, retinal ganglion cell
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