Topical Glucose-treatment Protects from Retinal Ischemic Damages by Cell Death Mode Switch

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Necrosis through cellular energy loss is presumed to expand by causing secondary damages of surrounding cells. In the low-density (LD) culture under the serum-free condition without any supplements, cortical neurons rapidly die in necrosis. The high-glucose treatment delayed the neuronal death by suppressing necrosis, but induced apoptosis through increase in Bax levels, cytochrome c release, caspase-3 activation. Although pyruvate as well as high-glucose inhibited necrotic cell death and rapid decrease in intracellular ATP levels under the serum-free condition, it did not induce apoptosis. In *in vivo* retinal ischemic model, retinal cells rapidly die by necrosis, followed by apoptosis. The maximum occurrence of necrosis and apoptosis were found 1 and 3 days after the stress. The topical application of glucose protected from the damages at the day 7 after the stress by inhibiting both necrosis and apoptosis. Remarkable retinal protection was observed when glucose, but not pyruvate was applied even 24 h after the ischemic stress. The co-pretreatment with herbimycin A, a non-selective tyrosine kinase inhibitor, inhibited the glucose-induced phosphorylation of Akt. Following herbimycin A-pretreatment, glucose-induced protection was partially attenuated, but apoptotic features were found at the day 1. All these findings suggest that the topical glucose protects from ischemia-induced retinal cell damages by switching the necrosis to apoptosis, which in turn is inhibited by unidentified neurotrophic factors.