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## **Erythropoietin modulation of astrocyte water permeability as a component of neuroprotection.**

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### **Abstract**

Disturbed brain water homeostasis with swelling of astroglial cells is a common complication in stroke, trauma, and meningitis and is considered to be a major cause of permanent brain damage. Astroglial cells possess the water channel aquaporin 4 (AQP4). Recent studies from our laboratory have shown that glutamate, acting on group I metabotropic glutamate receptors (mGluRs), increases the permeability of astrocyte AQP4, which, in situations of hypoxia-ischemia, will increase astrocyte water uptake. Here we report that erythropoietin (EPO), which in recent years has emerged as a potent neuro-protective agent, antagonizes the effect of a group I mGluR agonist on astrocyte water permeability. Activation of group I mGluRs triggers fast and highly regular intracellular calcium oscillations and we show that EPO interferes with this signaling event by altering the frequency of the oscillations. These effects of EPO are immediate, in contrast to the neuroprotective effects of EPO that are known to depend upon gene activation. Our findings indicate that EPO may directly reduce the risk of astrocyte swelling in stroke and other brain insults. In support of this conclusion we found that EPO reduced the neurological symptoms in a mouse model of primary brain edema known to depend upon AQP4 water transport.