The cytotoxicity of acidosis in rat cortical astrocytes caused an increase in ADP/ATP ratio and mitochondrial hyperpolarization

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Lack of oxygen in brain ischemia would switch the cells to anaerobic glycolysis. Extracellular pH thus drops and such acidosis causes neuronal cell death. The fate of astrocytes in acidosis is less studied. In our study, we investigated the signaling in acidosis challenged rat cortical astrocytes and whether these signals were related to mitochondrial dysfunction and cell death.

Exposure to acidic pH (6.8, 6.0) caused Ca^{2+} release and influx, p38 MAPK activation, and Akt inhibition. Mitochondrial membrane potential was hyperpolarized after astrocytes were exposed to acidic pH as soon as 1h and lasted for 24h. Such mitochondrial hyperpolarization was prevented by SC79 (an Akt activator) but not by SB203580 (a p38 inhibitor), suggesting that only the perturbation in Akt signaling was causally related to mitochondrial hyperpolarization. Acidic pH suppressed reactive oxygen species (ROS) production, thus ruling out the role of ROS in cytotoxicity. Interestingly, pH 6.8 caused an increase in ADP/ATP ratio and apoptosis; severe acidosis pH 6.0 caused a further increase in ADP/ATP ratio and necrosis.

Acidosis, possibly via Akt signaling suppression, caused mitochondrial hyperpolarization, together with other yet unidentified factors, might contribute to ATP depletion, consequently severe enough to cause necrotic cell death at severe acidosis pH 6.0 in astrocytes

Our study shown that astrocyte cell death in acidosis did not result from mitochondrial potential collapse; in case of severe acidosis at pH 6.0, necrosis might partly result from mitochondrial hyperpolarization and subsequent suppressed ATP production. These finding may have a significant implication for clinical consideration.

Keywords: Astrocytes; acidosis; Akt; mitochondria hyperpolarization.

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