Optogenetic glial alkalization relieves ischemic brain damage
-Mechanism and control of glutamate release from astrocytes

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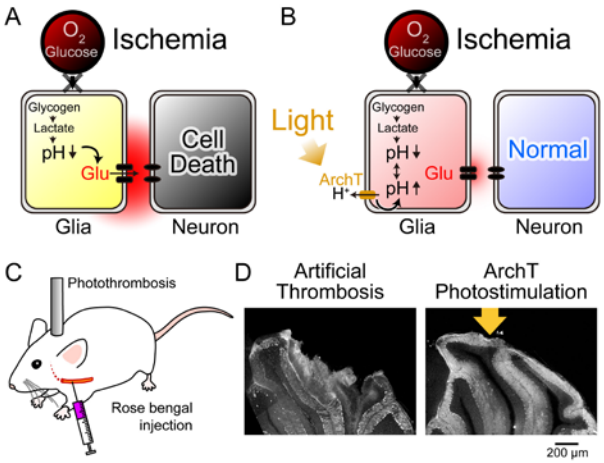
Research by Ko Matsui at the Division of Interdisciplinary Medical Science and his colleagues has shown that excess release of glutamate from non-neuronal cells, the glial cells, leads to brain deterioration upon ischemia. The key trigger of this release is glial acidification, and the release can be effectively stopped by countering the acidification with optical activation of a transgenetically expressed proton pump. These findings are presented in Neuron, published on January 22.

Liberation of excess glutamate upon ischemia is the direct trigger of neuronal cell death; however, the cellular source of glutamate and its release mechanism were unidentified. The group focused on the astrocytes of the glial cell population as they are the first responders to ischemic stress. When aerobic metabolism shuts down as a consequence of oxygen and glucose deprivation, lactate production from glycogen stored predominantly in glial cells continues, which leads to severe acidosis. Neuronal cell death via glutamate excitotoxicity follows. The group simply connected these two events and hypothesized that glial acidosis triggers glial glutamate release.Light-sensitive channels or pumps, originally found in algae or archaebacteria, can be exogenously expressed in mammalian cells and are used in recent studies as tools for controlling membrane potential. However, the fact largely ignored by the neuroscientists applying the optogenetic technique is that the major cation that flows through the widely used channelrhodopsin-2 (ChR2) and archaerhodopsin-T (ArchT) is proton. Thus, ChR2 and ArchT could be regarded as optogenetic tools for instant intracellular acidification and alkalization, respectively. The group showed that optical activation of ChR2 expressed in glial cells led to glial acidification and to the release of glutamate. On the other hand, glial alkalization via optogenetic activation of a proton pump, ArchT, led to cessation of glutamate release and to the relief of ischemic brain damage in vivo.Direct application of this technique in patients is limited as it would require preemptive gene therapy before ischemia. However, based on these findings, methods aimed at delivering strong intracellular pH buffer, development of drugs that enhances H+ extrusion mechanisms, or designing of glutamate-releasing anion channel blocker could be sought to alleviate brain damage upon ischemia.



Optogenetic countering of glial acidosis suppresses glial glutamate release and ischemic brain damage.

Beppu K, Sasaki T, Tanaka KF, Yamanaka A, Fukazawa Y, Shigemoto R, Matsui K.
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