Ischemia and Toxicity, When Ca^{2+} Signaling is Too Much of a Good Thing

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With myriad pathways involving Ca^{2+}, it is not surprising that a loss of Ca^{2+} homeostasis is implicated in cell death in response to trauma or chronic brain disease. For trauma, the therapeutic question is one of how to develop appropriate neuroprotective pharmacological cocktails to block necrosis and apoptosis. Experimental results of the last three decades suggest that it will be necessary to reexamine the simple "calcium overload hypothesis" and determine the degree to which Ca^{2+} elevation by different routes is involved in cell death, and how associated damage from each can be minimized.

Ischemic stroke interrupts the blood supply and results in oxygen and glucose deprivation to both neurons and glia (see Ch. 35). At the core of the insult is necrosis of all cell types, and extending outward is a variable region of compromised cells. Since much of brain metabolism has been taken over by astrocytes, the glia are more likely to survive even in regions where neurons are lost. The glia are far from benign, and there is evidence in model systems that they contribute to neuronal death in the region surrounding the initial infarct. Elevated Ca^{2+} waves propagate through the astrocyte syncytium either by the serial release of ATP on neighboring cells, and activation of the P2X receptors, or by Ca^{2+} carried through gap junctions between cells. As a result glutamate is released from the astrocytes and gates the neuronal NMDARs. The metabolically compromised neurons are depolarized, the Mg^{2+} block of the channel is largely absent, and the result is massive Ca^{2+} influx. The neuronal Ca^{2+} elevation by this pathway is the best studied, but numerous clinical approaches targeting these receptors have largely failed to be neuroprotective (Kalia et al., 2008). These results force us to reexamine alternative therapeutic strategies.

Since the goal is to avoid cell death, a logical place to start is the mitochondria. It is known that neuronal Ca^{2+} overload leads to mitochondrial Ca^{2+} accumulation, which decreases the electrochemical gradient and the production of ATP at precisely the moment when PMCA and SERCA are most needed to effectively export or sequester Ca^{2+}. In addition prolonged mitochondrial Ca^{2+} elevation leads to generation of reactive oxygen species and evokes opening of the mitochondrial permeability transition pore, with a subsequent release of cytochrome c and activation of caspases resulting in apoptosis (Murphy et al., 1999) (see Ch. 37). Thus neuroprotection may ultimately rely on preventing mitochondrial damage by Ca^{2+} to block the release of mediators of necrosis and apoptosis. In addition, the neuronal Ca^{2+} elevation will activate calpains, the Ca^{2+}-dependent proteases that cleave the NCX, SERCA, IP_3R, RyR, etc., all proteins involved in regulating Ca^{2+} homeostasis. This effectively locks the neurons into a state of elevated Ca^{2+}. Since influx and efflux pathways are both disabled by the calpains, one can imagine that blocking proteolysis of the efflux pathways might be neuroprotective. Finally, as noted above, many therapies target voltage- and ligand-operated influx, but efflux via transporters and pumps should be examined as well. During prolonged depolarization the neuronal NCX would be lethal, since it loads the cell with Ca^{2+} as it extrudes Na^{+}. Upon repolarization, under hypoxic conditions and low ATP, the NCX is neuroprotective since it is still able to extrude Ca^{2+} when activity of the PMCA pump has been compromised. This suggests transporter therapies would be complex, but a voltage-dependent block might be in order, so at depolarized potentials NCX would be blocked to prevent damage, but would be unblocked and active to export Ca^{2+} when the cell repolarizes.

As suggested by this brief list, the targets for potential neuroprotective therapies are vast, and the ultimate cocktail will likely address multiple Ca^{2+} cascades. But in closing it bears

emphasizing that the most obvious targets for potential therapy may not be neurons, but instead the glia, the metabolic support for the brain. Pharmacologically limiting the propagating Ca^{2+} waves may in the end be the best means of protecting their excitable neuronal neighbors and restricting the long-term damage to the circumscribed region of the initial insult.

References

Kalia et al., 2008 L.V. Kalia, S.K. Kalia, M.W. Salter, NMDA receptors in clinical neurology: Excitatory times ahead. Lancet Neurology. 7 (8) (2008) 742–755.

Murphy et al., 1999 A.N. Murphy, G. Fiskum, M.F. Beal, Mitochondria in neurodegeneration: Bioenergetic function in cell life and death. Journal of Cerebral Blood Flow and Metabolism. 19 (3) (1999) 231–245.