Intracerebral Hematoma
Beyond the Mass Lesion

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See related article, pages 2457-2462.

The signs and symptoms of acute intracranial hemorrhage are those of a rapidly developing mass lesion, compounded over time by surrounding edema, and sometimes by brain herniation. These are dramatic, debilitating, and often fatal events, but does the pathophysiology of intracranial hemorrhage extend beyond that of mass effect? Blood contains several factors that are potentially, and in some cases definitively, neurotoxic. Chief among these are hemoglobin and its breakdown products, heme and iron, which exhibit neurotoxicity at low micromolar concentrations through mechanisms involving iron-catalyzed production of reactive oxygen species. Brain has a variety of defense mechanisms to prevent the formation of reactive iron from blood hemoglobin, including inducible and constitutive heme oxygenases and iron-binding proteins, but these are easily overwhelmed by brain hemorrhage. Direct evidence for hematoma toxicity on surrounding brain has come from studies showing reduced extraction of blood oxygen by perihematoma brain tissue. Given that heme and iron are potent mitochondrial toxins, one explanation for reduced oxygen use in the vicinity of a brain hematoma is a reduced capacity for oxygen use by mitochondria in this region.

The study by Kim-Han et al provides additional support for this idea. This study measured rates of oxygen use by mitochondria isolated from the margins of intracerebral hematomas in 6 human subjects. These measurements revealed a roughly 40% reduction in state 3 respiration and 3-fold increase in state 4 respiration in perihematoma samples, relative to putatively normal mitochondria taken from epilepsy surgery sites. State 3 respiration is a measure of oxygen use during production of ATP from ADP, and thus approximates mitochondrial function under normal conditions in situ. State 4 respiration is a measure of oxygen consumption in the absence of ADP substrate, and hence provides a measure of the “leakiness” of mitochondrial membranes, which increases with mitochondrial damage.

Although neither of these measures alone reached a P value of 0.05, the use of tissue from human surgical resections unavoidably introduces variability into the study. The patients were of differing ages and with differing underlying diseases. Mitochondria were taken from several different brain regions, with variable ratios of neuronal and non-neuronal mitochondria. Large changes in neuronal mitochondria may be masked by smaller changes in more resilient glial cells, or by the extended time interval between resection and respiration measurements. All of these factors tend to introduce “noise” into the results, but the key question, not definitively addressed by these studies, is whether the observed mitochondrial dysfunction is attributable primarily to local trauma and mass effect, or is in fact attributable to diffusible factors from the hematoma. The findings by Kim-Han et al set the stage for future work in which interventions that target mitochondrial damage can be assessed to more clearly delineate the cause-effect relationships suggested by this work.

Disclosures

None.

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