Neuropathophysiology of Brain Injury

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KEYWORDS

• Mechanisms of ischemic brain injury • Excitotoxicity • Oxidative stress
• Neuroinflammation • Apoptosis • Synaptic plasticity • Neurovascular unit
• Translation

KEY POINTS

- Every year in the United States, millions of individuals incur ischemic brain injury from stroke, cardiac arrest, or traumatic brain injury. These forms of acquired brain injury can lead to death, or in many cases long-term neurologic and neuropsychological impairments.
- The mechanisms of ischemic and traumatic brain injury that lead to these deficiencies result from a complex interplay of multiple interdependent molecular pathways that include excitotoxicity, acidotoxicity, ionic imbalance, oxidative stress, inflammation, and apoptosis.
- This article briefly reviews several of the traditional, well-known mechanisms of brain injury and then discusses more recent developments and newer mechanisms.
- Although much is known concerning mechanisms of injury and the manipulation of these mechanisms to result in protection of neurons and increased behavioral performance in animal models of injury, it has been difficult to translate these effects to humans. Attention is given to why this is so and newer outcome measures of injury are discussed.

Every year in the United States, millions of individuals incur ischemic brain injury from stroke, cardiac arrest, or traumatic brain injury (TBI). These forms of acquired brain injury can lead to death, or in many cases long-term neurologic and neuropsychological impairments. The mechanisms of ischemic and traumatic brain injuries that lead to these deficiencies result from a complex interplay of multiple interdependent molecular pathways that include excitotoxicity, acidotoxicity, ionic imbalance, oxidative

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MECHANISMS OF INJURY FOLLOWING BRAIN ISCHEMIA

Excitotoxicity

The glutamate excitotoxicity hypothesis of ischemic cell damage suggests that injury is triggered by glutamate, an excitatory amino acid, released during ischemia from the intracellular compartment into the extracellular environment.[1] Glutamate is a major transmitter in the nervous system and, in addition to being required for rapid synaptic transmission for neuron-to-neuron communication, glutamate plays important roles in neuronal growth and axon guidance, brain development and maturation, and synaptic plasticity. Under normal physiologic conditions, the presence of glutamate in the synapse is regulated by active ATP-dependent transporters in neurons and glia. However, if these uptake mechanisms are impaired by metabolic disturbances brought about by ischemia, glutamate excessively accumulates, stimulating sodium (Na^+) and calcium (Ca^{2+}) fluxes into the cell through glutamate receptors, thereby injuring or killing the cell. Glutamate activates different types of ion channel–forming receptors (ionotropic) and G-protein–coupled receptors (metabotropic) that have an important role in brain function. The major ionotropic receptors activated by glutamate are commonly referred to as the *N*-methyl-D-aspartic acid (NMDA), alpha-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA), and kainic acid receptors. The ionotropic receptors are ligand-gated ion channels permeable to various cations. Overactivation of these receptors leads to an increase in intracellular Ca^{2+} load and catabolic enzyme activity, which can trigger a cascade of events leading to apoptosis and necrosis. These events can include membrane depolarization, production of oxygen free radicals, and cellular toxicity. NMDA and AMPA receptor antagonists showed great promise for providing neuroprotection in animal models, but have failed to translate clinically. One complication with this approach is the unwanted side effects associated with blocking receptors that are critical for normal brain function. Alternative approaches are now being considered, such as using partial NMDA antagonists such as memantine[2] or blocking receptor interactions with postsynaptic scaffolding molecules postsynaptic density protein 93/95.[3,4] Therapies targeting molecules downstream of NMDA receptors, such as calcium-calmodulin–dependent protein kinase (CAMKII) and death-associated protein kinase (DAPK) may also hold promise for limiting the excitotoxic cascade. In contrast, metabotropic receptors (metabotropic glutamate receptors [mGluRs]) are G-protein–coupled receptors that have been subdivided into 3 groups, based on sequence similarity, pharmacology, and intracellular signaling mechanisms. The role of mGluRs in brain injury is complex; however, most of the evidence points to a neuroprotective role, likely via antiapoptotic signaling and decreased excitability countering excitotoxicity.

Acidotoxicity

Metabolic acidosis can occur as a result of lactate accumulation during and following ischemia, or when mitochondrial respiration is dysfunctional. Acid-sensing ion