Calcium in Ischemic Cell Death

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Background—This review article deals with the role of calcium in ischemic cell death. A calcium-related mechanism was proposed more than two decades ago to explain cell necrosis incurred in cardiac ischemia and muscular dystrophy. In fact, an excitotoxic hypothesis was advanced to explain the acetylcholine-related death of muscle end plates. A similar hypothesis was proposed to explain selective neuronal damage in the brain in ischemia, hypoglycemic coma, and status epilepticus.

Summary of Review—The original concepts encompass the hypothesis that cell damage in ischemia-reperfusion is due to enhanced activity of phospholipases and proteases, leading to release of free fatty acids and their breakdown products and to degradation of cytoskeletal proteins. It is equally clear that a coupling exists between influx of calcium into cells and their production of reactive oxygen species, such as ·O2-, H2O2, and ·OH. Recent results have underscored the role of calcium in ischemic cell death. A coupling has been demonstrated among glutamate release, calcium influx, and enhanced production of reactive metabolites such as ·O2-, ·OH, and nitric oxide. It has become equally clear that the combination of ·O2- and nitric oxide can yield peroxynitrate, a metabolite with potentially devastating effects. The mitochondria have again come into the focus of interest. This is because certain conditions, notably mitochondrial calcium accumulation and oxidative stress, can trigger the assembly (opening) of a high-conductance pore in the inner mitochondrial membrane. The mitochondrial permeability transition (MPT) pore leads to a collapse of the electrochemical potential for H+, thereby arresting ATP production and triggering production of reactive oxygen species. The occurrence of an MPT in vivo is suggested by the dramatic anti-ischemic effect of cyclosporin A, a virtually specific blocker of the MPT in vitro in transient forebrain ischemia. However, cyclosporin A has limited effect on the cell damage incurred as a result of 2 hours of focal cerebral ischemia, suggesting that factors other than MPT play a role. It is discussed whether this could reflect the operation of phospholipase A2 activity and degradation of the lipid skeleton of the inner mitochondrial membrane.

Conclusions—Calcium is one of the triggers involved in ischemic cell death, whatever the mechanism.

Key Words: calcium • cerebral ischemia • free radicals • mitochondria