Ischemic Preconditioning

Introduction

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The quest for effective therapeutics for the treatment of stroke has resulted in more than a dozen clinical trials of putative neuroprotective drugs. None has proven successful. Although trial design may be a factor in these failures, the negative results of these attempts to find effective exogenous therapies for cerebral ischemia have stimulated research for endogenous modulators of neuroprotection. Such endogenous modulators produce the phenomenon of ischemic tolerance/preconditioning. Thus, stressors seem capable of producing a dose–response relationship in the brain where mild to severe preconditioning. Thus, stressors seem capable of producing a dose–response relationship in the brain where mild to severe stress first produces the tolerance phenomenon and increasingly severe stress culminates in apoptosis and finally necrosis.1 Tolerance-inducing stress may require an intensity resulting in some degree of injury at a cellular level, eg, protein denaturation.

The tolerance inducing stimulus may result from diverse stressors, including global ischemia, focal ischemia, hyperbaric oxygenation, inflammation, epileptic seizures, cortical spreading depression, hypothermia, hyperthermia, or cerebellar stimulation. The relevance to ischemic neuroprotection is found in the multiple examples of “cross-tolerance” described in which the tolerance-inducing stress protects against a different potentially injurious stress, eg, brief seizures protect against ischemia and mild degrees of ischemia protect against epileptic brain injury.

Although it is generally assumed that the preconditioning phenomenon was first described in the heart in the 1980s2,3 and not until 19904 in the brain, whole body traumatic stress producing “resistance” to subsequent trauma was described in 1943.5 Whereas the experiments regarding trauma might involve multiple organs in addition to brain, tolerance in brain to ischemia was described in 1964, 20 years before the classic cardiology experiments were published. In these 1964 studies, Dahl6 showed that anoxic pre-exposure protected against subsequent prolonged anoxic exposure. Further, in 1986 Schurr7 demonstrated “adaptation” of brain to anoxia in vitro. The words “preconditioning” and “tolerance” came from the 1964 article by Janoff8 who was studying lysosomes in a model of shock.

These endogenous protective mechanisms appear to function in multiple organs and in whole animals, including mammals, during hypoxic states. Examples include hibernation and hypoxia-tolerant states.9,10 Tolerance has been hypothesized to have a neuroprotective role in cerebral ischemia.11 More importantly, understanding tolerance may well lead to the development of small molecules or other methods of modulating the brain’s response to ischemia.

This session therefore addresses tolerance in the heart and the brain at the cellular level and at a genomic level. The clinical literature addressing the potential of transient ischemia to produce a preconditioning phenomenon is reviewed.

References

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