activate voltage-sensitive calcium channels (VSCC). In vitro experiments have established that calcium influx through VSCCs can lead to rapid transcriptional activation of immediate early genes (IEGs), a class of genes involved in signal transduction to the nucleus. Other stimuli, such as activation of the N-methyl-D-aspartate receptor, can also elicit IEG expression. Once induced, IEG mRNAs are shuttled to the cytoplasm and translated into proteins, e.g., FOS or JUN. These proteins reenter the nucleus, bind to their target genes, and regulate their transcription. Distinctive compensatory changes in neuronal gene expression appear to be mediated by the specific IEGs induced. A large number of these have now been identified, and a significant effort is now aimed at describing the specific IEGs induced over time in different ischemic models, with the goal of distinguishing IEGs that may lead to protection from those that may signal or induce cell death.

An and colleagues, by using a model of transient reversible focal ischemia, recently showed that jun B and c-fos mRNAs were induced by ischemia, and their relative concentrations were significantly higher at 60 minutes of reperfusion. The authors showed that the increase in IEG expression was associated with a fourfold to sixfold increase in the activity of the transcription factor AP-1, which may in turn induce the expression of late response genes such as those that lead to the production of growth factors. While it is clear that some IEGs may modify the postischemic cerebral environment in potentially protective ways, Smeyne and colleagues showed in nonischemic models that c-fos will appear just before histological evidence of cell death. Using transient global ischemia in which a period of four-vessel occlusion is subsequently followed by selective vulnerability of striatal and CA1 neurons, Wessel and colleagues showed that the CA1 region developed an early and late c-fos signal after ischemia. It should soon be possible to experimentally modify the regional concentrations of one or more of these mRNAs to test for the protective or destructive effect that each may mediate.

Heat-shock protein (HSP) is also likely to play a role in neuronal protection from ischemia. Since HSP mRNA does not contain an AP-1 site, its regulation is probably distinct from that of IEGs. Induction of HSP was shown to be protective in retinal cells. Using cell culture studies, Lowenstein et al suggested that stress proteins may have a protective role in excitotoxicity. Kirino and his colleagues were able to induce tolerance to ischemia in the gerbil hippocampus and correlated it with the induction of HSP. This protein is known to rise regionally after ischemia and may thus possess neuroprotective properties that can be experimentally modified.

It is clear, then, that a brain region that has been exposed to an episode of transient ischemia can rapidly set in motion mechanisms that may lead to long-term alterations in its structural and functional protein composition. At least some of these changes may be neuroprotective, and others may carry cell death programs. The experimental challenge is to identify these factors and test the effect of modifying them on cell survival.

At the clinical level, the occurrence of a TIA identifies the patient as being at increased risk of developing a stroke, but TIs have never been studied from the perspective that they may increase the brain's resistance to subsequent ischemic events. Patients who have a single TIA face a smaller (and a declining) risk of serious vascular events than those who have recurrent ones. These data call for further analysis to see if, akin to the protection from those that may signal or induce cell death.

Letters to the Editor

Can Transient Ischemic Attacks Have a Cerebroprotective Role?

To the Editor:

I would like to offer for reflection a hypothesis that is bound to be controversial, namely, that under some circumstances a transient ischemic attack (TIA) may set up conditions for a higher cerebral threshold for ischemia. It is reasonable, then, to conclude that at least in animal experiments, transient episodes of ischemia that do not cause damage may under some circumstances be neuroprotective. These data suggest that short-lasting ischemic episodes probably upregulate enzymatic and other protein synthetic activities that can ultimately confer protection.

It is now clear that in response to short-lasting stimuli at its surface the cell can activate genes that may lead to alterations in its protein composition. We have shown in animal studies in vivo that transient ischemia such as occurs during a TIA can reversibly activate voltage-sensitive calcium channels (VSCC). In vitro experiments have established that calcium influx through VSCCs can lead to rapid transcriptional activation of immediate early genes (IEGs), a class of genes involved in signal transduction to the nucleus. Other stimuli, such as activation of the N-methyl-D-aspartate receptor, can also elicit IEG expression. Once induced, IEG mRNAs are shuttled to the cytoplasm and translated into proteins, e.g., FOS or JUN. These proteins reenter the nucleus, bind to their target genes, and regulate their transcription. Distinctive compensatory changes in neuronal gene expression appear to be mediated by the specific IEGs induced. A large number of these have now been identified, and a significant effort is now aimed at describing the specific IEGs induced over time in different ischemic models, with the goal of distinguishing IEGs that may lead to protection from those that may signal or induce cell death.

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It is clear, then, that a brain region that has been exposed to an episode of transient ischemia can rapidly set in motion mechanisms that may lead to long-term alterations in its structural and functional protein composition. At least some of these changes may be neuroprotective, and others may carry cell death programs. The experimental challenge is to identify these factors and test the effect of modifying them on cell survival.

At the clinical level, the occurrence of a TIA identifies the patient as being at increased risk of developing a stroke, but TIs have never been studied from the perspective that they may increase the brain's resistance to subsequent ischemic events. Patients who have a single TIA face a smaller (and a declining) risk of serious vascular events than those who have recurrent ones. These data call for further analysis to see if, akin to the protection from those that may signal or induce cell death.

References

any cerebral protection that a TIA may confer is probably limited to the affected region. Only about half of anterior circulation strokes that follow a TIA occur in the same vascular territory. Considering that this figure includes patients with ipsilateral focal vessel stenoses known to be associated with subsequent strokes on a hemodynamic basis, the coincidence of the vascular territory between a TIA and a subsequent stroke may be small, again suggesting that a TIA in one region may confer upon it some protection from subsequent permanent ischemic damage. Formal testing of this hypothesis using large patient databases would be desirable.

The hypothesis presented here that transient cerebral ischemia may induce endogenous responses that are potentially neuroprotective would suggest that present therapeutic modalities in cerebral ischemia are based on a limited perspective. N-Methyl-D-aspartate or kainate/quisqualate receptor antagonists, calcium channel blockers, and other therapeutic agents may have limited therapeutic efficacy as well if they interfere with the very triggers that induce subsequent endogenous protection. Methods to enhance the production of specific IEGs, increase the concentration of HSP, or resupply the brain with natural protectants such as growth factors may offer better prophylactic potential than is afforded by presently available methods. Finally, these considerations should not (for the moment, anyway) lead to deviations from present clinical practice until better alternatives arise from further study.

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References


The following response was written by invitation from the editors:

Dr Hakim's letter raises a point which is timely, provocative, and at the same time disturbing in that it takes emerging data from animal models and uses them to challenge time-honored clinical concepts. This is one of the important roles of animal experimentation. On the other hand, I suspect that the thought that TIAs might be neuroprotective has been entertained by most clinicians who have read data on postischemic gene expression but has been rejected because it flies in the face of logic and clinical experience.

Dr Hakim clearly summarizes the elegant studies unequivocally demonstrating that brief ischemic episodes can activate genes to result in the production of neuroprotective proteins. However, the evidence against a net protective role for TIAs includes the following: (1) of all risk factors, TIA is probably the strongest predictor of subsequent stroke; (2) an increasing number of TIAs increases the risk of stroke; (3) the more severe the TIA (i.e., the more prolonged, or the appearance of CT abnormalities), the higher the risk of subsequent stroke; and (4) the biochemical and hemodynamic consequences of severe ischemia as demonstrated in numerous molecular biological studies of the cascade of events occurring after either global or focal ischemia are overwhelmingly detrimental when compared with any protective defense established previously by protein induction after a TIA.

Dr Hakim suggests that the decline in incidence of stroke over time after a TIA suggests the brain's enhanced ability to withstand further insults. However, most experimental data indicate that inducible proteins have a finite existence. Is there any evidence from animal studies that these proteins afford protection months after a brief ischemic insult? It is more likely that the pathophysiologic events which caused the TIA (such as an episode of heightened platelet aggregation or atherosclerotic remodeling, cardiac arrhythmia, or mural thrombus) areameliorated over time.

These comments are not meant to detract from the importance or relevance of published or future investigations of gene expression after brain injury, and Dr Hakim should be applauded for his perceptive (and bravery) in using the provocative existing data on gene expression in animal models to challenge established and possibly erroneous clinical assumptions. His point that prophylactic N-methyl-D-aspartate antagonists or calcium blockers may impair one of the brain's important protective mechanisms seems particularly valid and clinically relevant and one that could be tested in experimental models. Even more provocative is the possibility to identify and either synthesize or stimulate the production of inducible neuroprotective proteins as a therapeutic strategy. However, the best clinical evidence is that one of the most effective ways to prevent a stroke is to prevent TIAs. Until the relative role of inducible neuroprotective proteins is understood in relation to the complex multifactorial process of TIA and...
Could transient ischemic attacks have a cerebroprotective role?
A M Hakim

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