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The new language of cerebral ischemia.

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Special Report

The New Language of Cerebral Ischemia

Myron D. Ginsberg, *Department of Neurology, Cerebral Vascular Disease Research Center and Neurotrauma Research Center, University of Miami (Fla) School of Medicine*

We stand at the dawn of a exhilirating era of extraordinary promise in our diagnostic and therapeutic approach to cerebrovascular disorders. Correspondingly, there has emerged a new "language" of cerebral ischemia, encompassing novel concepts with which we must now become conversant. The following is an attempt to set forth certain key rubrics of this glossary and to place them in pathophysiological perspective.

Threshold Phenomena in Cerebral Ischemic Injury

The recognition that crucial events in the pathogenesis of ischemic brain injury are set into motion at critical thresholds of reduced cerebral blood flow (CBF) constitutes a seminal conceptual advance with broad ramifications (see Hossman [1] for a recent review). In patients undergoing carotid endarterectomy, it was first observed that CBF reductions to approximately one third of normal (from about 0.5 to 0.16 or 0.17 mL/g per minute) led to electroencephalographic flattening (2, 3). Studies in baboons with acute middle cerebral artery (MCA) occlusion substantiated that cortical somatosensory evoked potentials ceased when CBF fell to 0.15 to 0.20 mL/g per minute (4). Microelectrode measurements, however, revealed that this suppression of evoked responses was not caused by altered extracellular $[K^+]$ or $[H^+]$ levels, because massive elevations of extracellular $[K^+]$ were observed only at much lower CBF (approximately 0.06 to 0.10 mL/g per minute). These findings thus pointed toward *dual* thresholds in ischemia: the higher one (approximately 35% of normal CBF) for functional suppression (ie, failure of synaptic transmission), and the lower one (at approximately 15% to 20% of normal CBF) for major cationic dyshomeostasis (ie, failure of energy-requiring ion pump mechanisms) (1, 5).

To the concept of CBF thresholds was added the notion of time dependence (6). By correlating microelectrode measurements of local cortical CBF within foci of MCA occlusion with subsequent histologic analysis in cats, these workers established a curvilinear relationship between intensity and duration of CBF decrements that predicted neuronal injury. Near-total reductions of CBF (as would occur in cardiac arrest with resuscitation) gave rise to neuronal damage after only a few minutes, while somewhat lesser decrements (as would typically occur in thromboembolic ischemic stroke [in which some collateral circulation is commonly present]) could be sustained for longer periods without permanent injury.

The Ischemic Penumbra

Without doubt, the ischemic penumbra has emerged as a concept of central import in our current understanding of focal ischemic lesions in the brain (7, 8). Named by analogy to the half-shaded zone surrounding a solar eclipse (5), the penumbra lies just peripheral to the core zone of a focal ischemic lesion. Ion-selective microelectrode studies of the cortex during experimental MCA occlusion have yielded the most rigorous characterization of the penumbra. In the neocortical region of the ischemic core (having CBF at or below approximately 20% of normal), extracellular $[K^+]$ undergoes rapid steady-state elevations after MCA occlusion, denoting anoxic depolarization—a sign of impending irreversible injury. In contrast, cortical sites peripheral to the core, in which CBF is somewhat higher (approximately 20% to 40% of normal), are electrically silent but do not develop steady-state elevations of $[K^+]_e$ (7–9).

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Address reprint requests to Myron D. Ginsberg, MD, Department of Neurology (D4-5), University of Miami School of Medicine, PO Box 016960, Miami, FL 33101.

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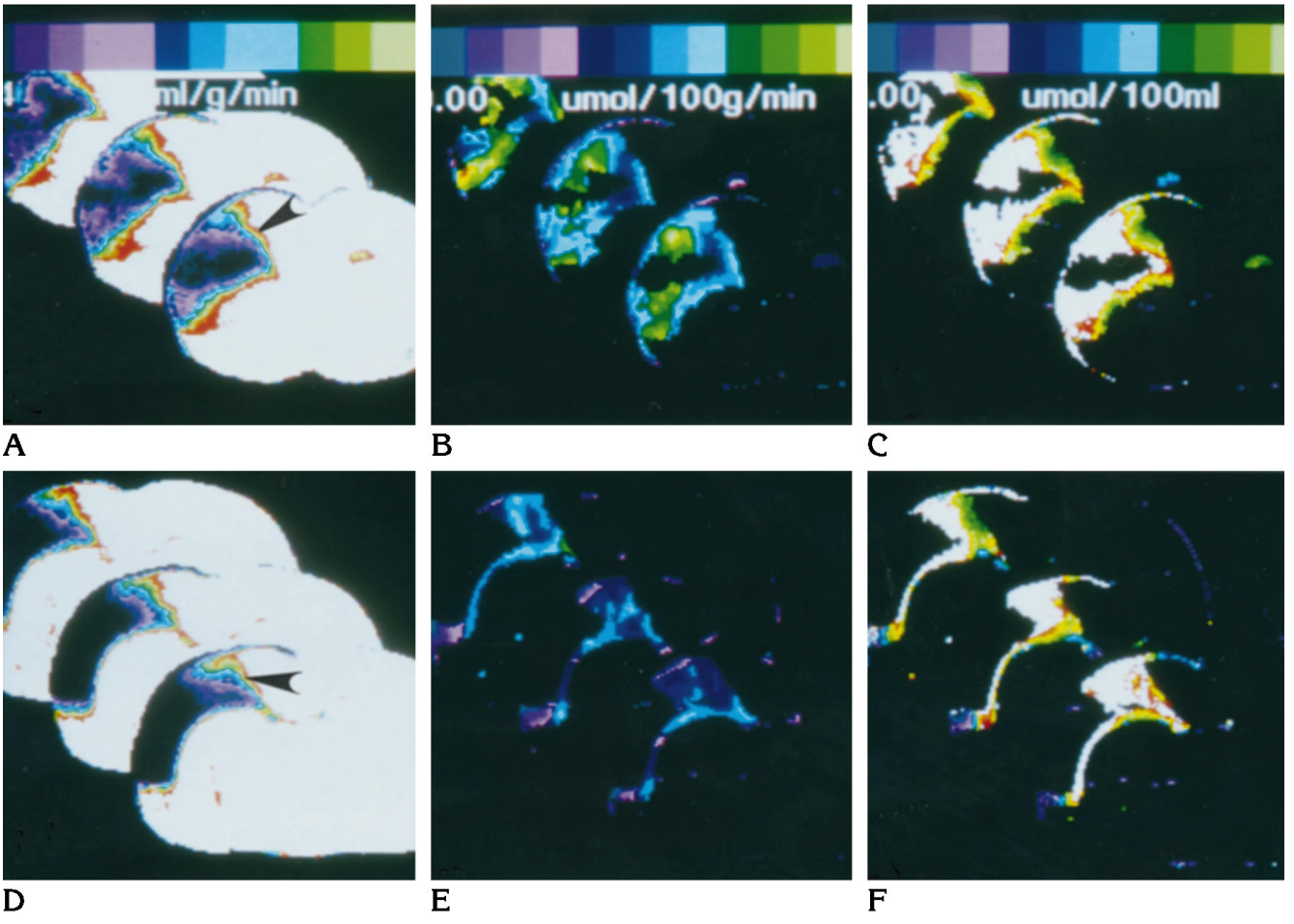


Fig 1. Averaged autoradiographic images of local CBF (ICBF, *A* and *D*), local cerebral glucose use (ICMRgl, *B* and *E*), and the ICMRgl/ICBF ratio (*C* and *F*). These image data sets were derived from matched series of rats (n = 7 each) studied for either ICBF or ICMRgl 1 hour after distal photothrombotic MCA occlusion. The panels of the *upper row* display 3 sequential images (separated by 100 μm) at the anterior pole of the ischemic lesion (coronal level, bregma +2.0 mm). The panels of the *lower row* depict 3 sequential images at the center of the ischemic focus (coronal level, bregma −1.1 mm). The ICBF data sets (*A* and *D*) are thresholded such that colored pixels represent values of 20% to 40% of control (0.23 to 0.47 mL/g per minute), corresponding to the ischemic penumbra (*arrowheads*). The ischemic core (ICBF <20% of control) is shown in *black*, and supraischemic regions are in *white*. The ischemic penumbra surrounds the core and is particularly concentrated at the poles of the ischemic lesion. ICMRgl (*B* and *E*) and the metabolism/flow ratio (*C* and *F*) are shown only for those penumbral pixels. The acute ischemic penumbra is the site of marked metabolism-greater-than-flow dissociation, such that the metabolism/flow ratio in the penumbra is elevated, on average, fourfold to fivefold above normal (*C* and *F*) (image data reprocessed from the study of Back et al [11]).

Thus, the penumbra lies below the CBF threshold for electrocortical silence but above that for massive ionic dyshomeostasis (10).

The various attributes of the ischemic penumbra bear close scrutiny because they are pivotal for grasping the essence of a focal ischemic lesion. They include the following:

1. *The size of the early ischemic penumbra is substantial.* In our experimental studies, in which affected tissue volumes were precisely computed by autoradiographic image-processing strategies (11, 12), the penumbra initially subsumed one half or more of the entire ischemic lesion (Fig 1A).
2. *The penumbra can be defined by its level of CBF,* which lies within a rather narrow range (as noted above, approximately 20% to 40% of normal [9, 11, 13, 14])—just slightly above that of the ischemic core (Fig 1A, D). Because cerebral autoregulation is not maintained in ischemic tissue, CBF and, hence, neural function in the penumbra are precariously dependent on small changes in perfusion pressure (8). As a result, *the penumbra is inherently unstable* and at potential risk of irreversible deterioration.
3. *The penumbra is electrophysiologically dynamic* in that it is the site of recurrent *ischemic depolarizations,* detectable as transient negative shifts of the cortical direct current (DC) potential (Fig 2) or as transient elevations of $[K^+]_e$ levels. Ischemic depolarizations have, by now, been convincingly documented in ex-

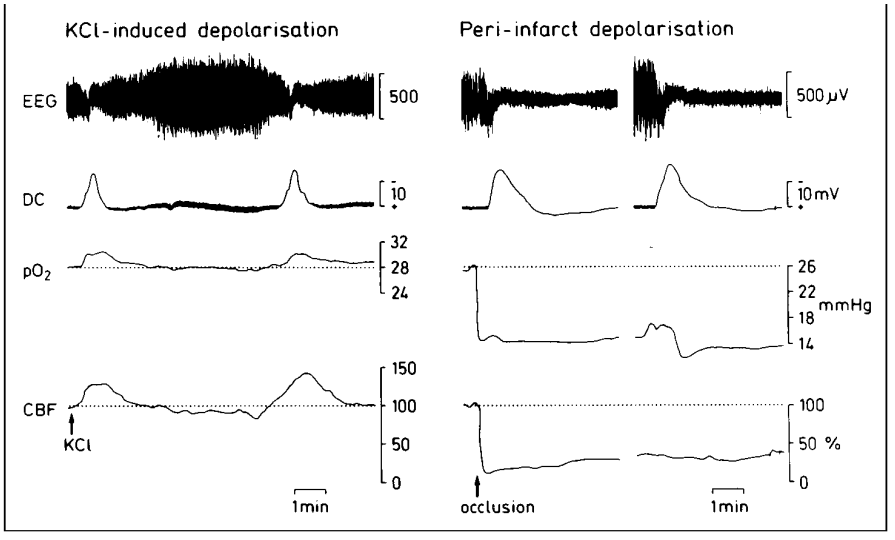


Fig 2. Electroencephalographic (*EEG*) recordings, direct current (*DC*) potential, cortical oxygen tension (P_{O_2}) and laser Doppler flow in the parietal cortex after spreading depression in intact rats (*left*), and after MCA occlusion (*right*). Data were recorded in the periphery of the MCA territory. During KCl-induced spreading depression in intact rats, regional CBF and tissue P_{O_2} increase. In contrast, ischemic depolarizations arise in tissue in which CBF is critically reduced and unable to increase; as a result, tissue P_{O_2} declines into the hypoxic range. Waves of ischemic depolarization tend to be broader than those of normal spreading depression (from Back et al [16]).

perimental studies (reviewed by Hossmann [15]). Unlike spreading depression, which these waves superficially resemble, ischemic depolarizations arise within cortical zones in which CBF is critically reduced and, hence, unable to increase in response to electrophysiological stimuli. Thus, tissue P_{O_2} (which characteristically increases during spreading depression in the normal brain) *declines* during ischemic depolarizations (16) (Fig 2). That ischemic depolarizations are deleterious to penumbral tissue has been proved by several studies showing reductions in infarct volume in response to glutamate antagonism at either *N*-methyl-D-aspartate (NMDA) (17) or non-NMDA (18) receptors, or in response to hypothermia (19), all of which reduce ischemic depolarizations. Conversely, when the number of ischemic DC shifts is doubled by inducing additional depolarizations after MCA occlusion, the total volume of ischemic injury increases (20) (Fig 3).

4. *The ischemic penumbra is thus metabolically unstable.* Measurements of penumbral tissue high-energy metabolites "freeze-trapped" in relation to ischemic depolarizations after MCA occlusion reveal approximately 50% reduction of cortical adenosine triphosphate (ATP) and phosphocreatine (PCr) levels during reversible waves of depolarization, and complete depletion of these metabolites on terminal anoxic depolarization (21).
5. *The ischemic penumbra is the site of severe metabolic stress.* This is evident from our studies in which we have applied three-dimensional autoradiographic image-averaging strategies (22, 23) to co-map local brain blood flow (ICBF), local glucose use (ICMRgl), and the "coupling ratio" (ICMRgl/ICBF) in matched series of rats studied in the first hour after MCA occlusion (Fig 1) (11, 12). Despite reduced ICBF, the early penumbra shows a normal or focally elevated glucose metabolic rate. As a consequence, the ICM Rgl/ICBF ratio is severely elevated, denoting heightened glycolytic turnover (likely, anerobic), markedly in excess of available perfusion. This inappropriate metabolic activity is likely being driven by

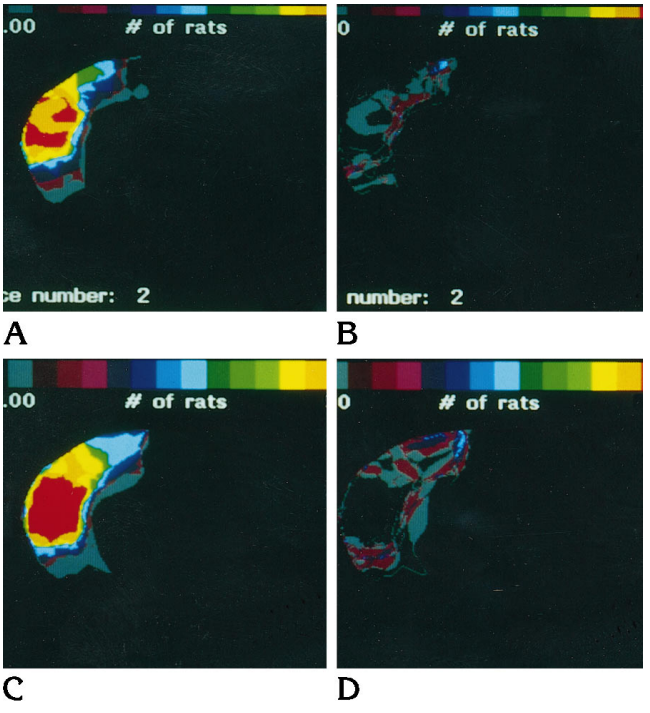
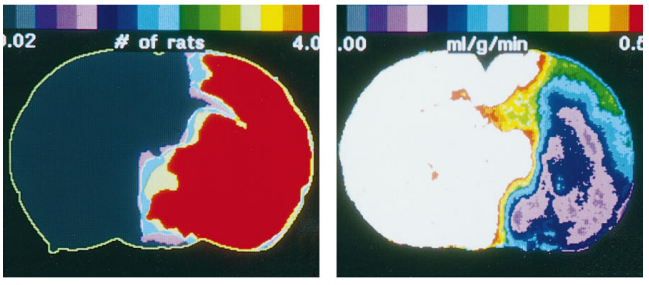


Fig 3. Histologic frequency maps illustrate zones of complete infarction (pannecrosis, *A* and *C*) and of "incomplete infarction" (selective neuronal necrosis, *B* and *D*) in rats with photothrombotic MCA occlusion. *A* and *B* are from MCA-occluded rats that had only spontaneous ischemic depolarizations. *C* and *D* are from MCA-occluded rats that, in addition, received induced depolarizations so as to double the total number of DC potential shifts. Rats with additional depolarizations show a trend toward more extensive infarcts (*C*), as well as a significantly enlarged zone of selective neuronal necrosis (*D*) (data derived from the studies of Back et al [20] and Alexis et al [108]).



A B

Fig 4. Data derived from rats subjected to 2-hour proximal MCA occlusion by insertion of an intraluminal filament. *A* is a computer-derived frequency map illustrating the distribution of histopathologic infarction on hematoxylin-eosin–stained sections of perfusion-fixed brains after 3-day survival. A consistent confluent zone of cortical and subcortical infarction is apparent. *B* is an averaged ICBF autoradiogram obtained at the end of a 2-hour period of MCA occlusion in this model, thresholded to illustrate flow in the ischemic core and penumbra. The core plus penumbral ICBF lesion at 2 hours precisely predicts the eventual distribution of histopathology (*A*) (data derived from Ginsberg et al [12]).

the need to synthesize ATP to restore the ionic dyshomeostasis induced by penumbral ischemic depolarizations (discussed above).

6. *The lifespan of the penumbra is therefore limited.* In our laboratory (12), ICMRgl and ICBF measurements made just 1 hour after a 2-hour period of transient MCA occlusion reveal already greatly suppressed ICMRgl and loss of the ICMRgl/ICBF uncoupling earlier observed—observations denoting devitalized tissue. In permanent MCA occlusion, cytoskeletal proteolysis is already advanced in the ischemic core by 2 hours, and in the penumbra by 3 to 4 hours (24). In sequential positron emission tomographic (PET) studies of cat MCA occlusion, elevated oxygen extraction fraction (denoting uncoupling of local oxygen metabolism and blood flow), present during the first 4 hours of MCA occlusion, has disappeared by 18 to 24 hours (25).
7. Thus, *the therapeutic window for reperfusion in ischemic stroke is quite narrow* (26, 27). In awake primates with local CBF monitoring, MCA occlusion leads to irreversible damage in loci in which CBF has fallen below 0.10 to 0.12 mL/g per minute during 2- to 3-hour MCA occlusion, or below 0.17 to 0.18 mL/g per minute in permanent MCA occlusion (28). Studies in cats (6) and rats (29, 30) yield a rather consistent picture: that MCA occlusion of 3 to 4 hours gives rise to maximal infarction, comparable to that seen with permanent occlusion (Fig 4). The consensus of these studies would predict that there is a window of opportunity of at most 3 to 4 hours within which reperfusion therapy would need to be initiated to be successful. The results of the recently completed National Institute of Neurologic Disorders and Stroke multicenter trial of thrombolysis for hyperacute ischemic stroke are consistent with this view: patients treated within 3 hours with alteplase were improved on neurologic and outcome measures at 3 months (31). By contrast, a large European trial of thrombolysis in which most patients were treated within a 4- to 6-hour interval failed overall to show a positive effect (32).

In apparent conflict with the results of the above reports, serial PET studies of patients with ischemic stroke have suggested in at least some instances that there are substantial volumes of tissue as late as 17 hours after stroke onset in which CBF and oxygen extraction fraction are in the penumbral range and which have cerebral metabolic rate for oxygen ($CMRO_2$) values above the assumed viability threshold; chronic-stage PET studies reveal subsequent metabolic deterioration of these foci (33). Still other studies have suggested that potentially metabolically viable tissue in the border area of ischemia might exist as late as 48 hours after stroke onset (34). Notwithstanding the therapeutic optimism generated by these individual observations, these authors' own data (35) can be used to show that increased oxygen extraction fraction observed on PET scans in the 7- to 18-hour period after stroke onset does not, in fact, predict consistent tissue viability (36). Unfortunately, sequential quantitative multitracer PET studies are logistically extremely difficult to carry out during the crucial first 4 to 6 hours after stroke onset, and virtually no large patient series have been reported to date or are likely to be in the future. In this author's opinion, in designing clinical trials of putative neuroprotective agents, one would be gravely mistaken to assume that consistent metabolically viable tissue amenable to therapeutic intervention still exists after 4 to 6 hours.

Brain Temperature: A Key Modulator of Ischemic Injury

Although experimental studies of cerebral ischemia in animals conducted before 1987 generally monitored and regulated rectal temperature, virtually all of these studies failed to appreciate that brain temperature can vary independently of core body temperature during ischemia, and that even small degrees of brain temperature alterations crucially affect the outcome of ischemic insults. These points have now been clearly established. For example, in global forebrain ischemic insults typically lasting 5 to 20 minutes, the expected extensive destruction of vulnerable neuronal populations

in the CA1 sector of hippocampus and in the caudoputamen is markedly reduced (by 75% or more) by just a 2° to 3°C lowering of intraischemic brain temperature (37–39). In focal cerebral ischemia, particularly if temporary (eg, 90- to 120-minute middle cerebral artery occlusion), small degrees of temperature reduction are capable of diminishing the volume of infarction by 50% or more, indeed up to 70% to 80% (40–44), depending on the delay in initiating hypothermia, its duration, and its extent (26). Even mild degrees of intraischemic hypothermia completely suppress the massive release of glutamate into the brain's extracellular space. Hypothermia also modifies a variety of intracellular processes potentially germane to cerebroprotection.

Interestingly, moderate postischemic hypothermia, initiated quickly after a global insult, appears to protect neurons when only *short* survival periods are permitted before neuropathologic examination (45), but in contrast to the situation with *intra*ischemic hypothermia of similar degree, this protection is lost when 2-month survival is permitted (46). Nonetheless, by markedly delaying the process of cell death, postischemic hypothermia appears to widen the window of therapeutic opportunity so as to provide the opportunity for synergistic neuroprotection when delayed therapy with an NMDA antagonist (47) or a free-radical spin-trap agent (MY-T. Globus, W. D. Dietrich, I. Valdes, S. Kraydieh, M. D. Ginsberg, R. Busto, "The Combination of Postischemic Hypothermia and Delayed PBN Treatment Leads to Chronic Neuropathological Protection after Global Ischemia," *Society of Neuroscience Abstracts* 1996;22(part 1):1427) is instituted.

A by-product of the above studies is the realization that *even small degrees of brain temperature elevation are markedly deleterious* in the setting of brain ischemia or traumatic injury. Thus, raising brain temperature during global ischemia from 37°C to just 39°C has the effect of (*a*) strikingly augmenting the extent of ischemic injury and extending it to zones not ordinarily vulnerable, (*b*) accelerating the evolution of pathologic alterations, and (*c*) producing a marked multifocal breakdown of the blood-brain barrier (48–50). In models of MCA occlusion, mild hyperthermia markedly enlarges infarct volume. Indeed, even when a 3-hour period of moderate hyperthermia is imposed 1 day after a temporary period of focal (51) or global (52) ischemia, the resulting damage becomes far more extensive.

These experimental observations have stimulated the development of clinical protocols to measure brain temperature directly in brain-injured patients (53) and to initiate controlled multicenter clinical trials of moderate hypothermia for the treatment of acute traumatic brain injury. Although a randomized clinical trial of hypothermia in ischemic stroke has yet to be organized, clinicians are now broadly aware of the necessity to avoid temperature elevations assiduously in the acute period after ischemic or traumatic brain injury. Interestingly, the prospect of measuring regional brain temperature noninvasively by diffusion-weighted magnetic resonance (MR) imaging now exists.

The Molecular Biology of Cerebral Ischemia

A particularly exciting dimension of cerebral ischemia research in the 1990s is the growing contribution of molecular biology, to both our understanding of the pathophysiology of ischemic injury and the construction of novel therapeutic approaches. Space constraints permit only representative work to be cited.

Recent observations have confirmed that cerebral ischemia gives rise to widespread alterations of gene regulation and expression. For example, ischemia leads to the rapid expression of immediate-early genes of the c-*fos* and c-*jun* families, whose gene products interact to form fos-jun heterodimers that function as the so-called AP-1 transcription factor, regulating the expression of other genes. Focal ischemia triggers the prompt expression of c-*fos* and c-*jun* mRNA (54, 55), which peaks during early reperfusion, with 4- to 6-fold increases in AP-1 binding activity (54) (Fig 5). The latter may be suppressed in vivo by the intracerebroventricular administration of antisense c-*fos* oligodeoxynucleotides (56).

Cerebral ischemia and trauma also induce the expression of heat shock genes—so-called stress genes—in the brain (57). In focal cerebral ischemia, hsp70 mRNA is induced within 4 hours and persists for at least 24 hours. Interestingly, the hsp70 message is only patchily induced within the ischemic core but is markedly induced in neurons of the penumbra at 4 to 24 hours. Correspondingly, the strong expression of hsp70 protein in neurons of the penum-

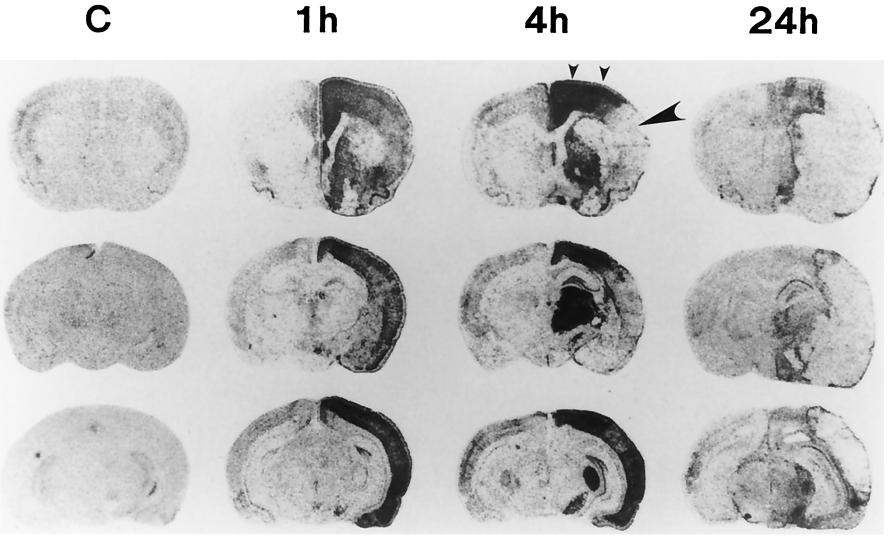


Fig 5. c-*fos* mRNA in situ hybridization autoradiograms of coronal brain sections from rats subjected to sham surgery (*C*) or MCA occlusion for 1, 4, or 24 hours. At 1 hour of occlusion, c-*fos* mRNA is induced throughout the ipsilateral cortex and caudoputamen except for the lateral caudoputamen. By 4 hours, there is a decrease of c-*fos* mRNA in the core of the ischemic region (*large arrowhead*), together with persistent induction in surrounding regions of ipsilateral cortex (*small arrowheads*) and in some portions of the contralateral cortex. c-*fos* mRNA is also induced in the ipsilateral thalamus, substantia nigra, and hippocampus at 4 hours. The induction in these regions disappears by 24 hours (from Kinouchi et al [55]).

bra at 24 hours allows it to serve as a reliable anatomic marker of that zone (58).

The study of ischemic mechanisms has been vastly abetted by the use of transgenic and knockout mouse mutants. The challenges imposed by physiological monitoring, blood sampling, and implementation of ischemia models in these tiny animals have been largely surmounted (59). There are several elegant examples of the use of transgenic and knockout mutant mice to establish the relevance of specific stroke mechanisms. For example, studies in transgenic mice with threefold overexpression of the enzyme CuZn superoxide dismutase have convincingly established the role of oxygen radical scavenging in diminishing neural injury after transient focal ischemia (60). In other studies of mutant (knockout) mice that fail to express the neuronal isoform of nitric oxide synthase (NOS), smaller infarcts develop and the mice have less severe neurologic deficits than normal mice (61). In contrast, knockout mice deficient in the endothelial form of NOS have larger infarcts than normal (62). Studies such as these have provided definitive answers to challenging mechanistic questions.

Therapeutically, there are already intriguing examples of targeted molecular-biological approaches to treatment of ischemia. Thus, antisense oligodeoxynucleotides to the NMDA-R1 component of the NMDA receptor channel complex, when given to rats with MCA occlusion, reduce the volume of ischemic infarction (63). In other studies, viral vectors have been used to introduce "therapeutic" genes into the central nervous system. Thus, overexpression of the glucose transporter gene via the introduction of a herpes simplex viral vector into the nervous system protected neurons from focal ischemic injury (64). In another study, the use of an adenoviral vector to induce central nervous system overexpression of receptor antagonist protein to the damaging cytokine, interleukin-1, led to reduction in stroke size (65). These studies are vanguard examples of what, in future years, might evolve into accepted therapeutic strategies!

Mechanisms of Cell Death: Apoptosis versus Necrosis

The traditional view is that neurons succumb to ischemia, whether focal or global, by a process of *necrosis* triggered by oxygen and glucose-substrate depletion. A large and rapidly accruing body of evidence suggests, however, that at least under some circumstances, ischemic neurons might also undergo *apoptosis*—an active, genetically regulated process of "programmed cell death" resembling that occurring during normal embryonic development and involutional atrophic processes, and in the course of immune-mediated cell killing (reviewed by Bredesen [66]). (The classic method of inducing apoptosis in cell culture is to withdraw neurotrophic factors.) Morphological hallmarks of apoptosis include early blebbing of the plasma membrane; margination of nuclear chromatin leading to "apoptotic bodies"; and internucleosomal fragmentation of DNA, giving rise to oligonucleosomal DNA fragments of approximately 180 base pairs visible as "ladder-

ing" on electrophoretic gels, and to DNA strand breaks demonstrable by in situ DNA nick-end labeling procedures (67). Mitochondria are structurally normal and inflammatory changes are absent (66).

After 2 hours of reversible focal ischemia (by MCA occlusion) in rats, DNA fragmentation is evident within ½ hour, peaks at 24 to 48 hours, and persists up to 4 weeks, with apoptotic changes evident chiefly at the inner boundary zone of the infarct (68, 69). After permanent MCA occlusion, DNA fragmentation is initially present in the infarct core and later expands in a radial fashion (70). Selective neuronal death exhibits apoptotic features, not only in global and focal ischemia, but also in cerebral trauma, epileptic brain damage, and injury induced by the human immunodeficiency virus–1 envelope protein GP120 (69, 71). These observations carry intriguing therapeutic implications as apoptosis requires active genetic programs and depends on protein synthesis. Exhaustive genetic studies in the nematode *C elegans* have revealed a panoply of genes, each regulating specific steps of the cell-death program. Homologs of these genes exist in mammalian systems and include bcl-2 (a suppressor), the interleukin 1β-converting enzyme (ICE) family (promotors), and cell-cycle genes such as p53.

The extent to which apoptotic processes are truly important in ischemic neuronal death has yet to be definitively established. For example, apoptotic features often coexist within or near foci of necrosis, and there is contradictory morphological evidence in global ischemia as to whether delayed death of hippocampal CA1 neurons is predominantly necrotic or apoptotic. The apparently rapid disappearance of apoptotic cells from tissue confounds efforts to quantitate the extent of their contribution. However, successes in reducing the size of focal cortical infarcts with the protein-synthesis inhibitor cyclohexamide (72) or by viral vector-induced bcl-2 overexpression (73) would argue that apoptosis is indeed important in contributing to ischemic injury. In cell culture, exposure of cortical neurons to short durations or low concentrations of the excitotoxin NMDA or to substances generating low levels of the toxic anion peroxynitrite induces delayed neurotoxicity with predominantly apoptotic features (74). On the basis of such evidence, one can speculate that apoptotic death might be important in *less severe* or *more chronic* contexts—for example, in the ischemic penumbra, after short periods of ischemia, in brains chronically deprived of collateral circulation (eg, by multivessel atheromatous occlusive disease), or under conditions of mild but but prolonged hypoxia/oligemia.

Imaging of Human Stroke Pathophysiology

The experimental advances reviewed above have been paralleled in recent years by the technological development of astonishing methods of depicting zones of cerebral ischemia at their earliest stages in the human brain by diffusion-weighted and hemodynamically weighted MR imaging. Diffusion-weighted methods are sensitive to the net movement of water, for which diffusion barriers exist in tissue by virtue of its structural constituents and the chemical interactions between water and macromolecules (75). Localizing hyperintensities appear on diffusion-weighted MR images within minutes of the onset of cerebral ischemia, with diffusion declining by 40% to 50% (76, 77). This rapidly appearing diffusion-weighted hyperintensity and the decrease in the apparent diffusion coefficient (ADC) correspond to the time course of decline of tissue high-energy compounds and the consequent failure of the energy-requiring K^+, Na^+-ATPase pumps. The latter is the key event that initiates cytotoxic edema (ie, the movement of water and Na^+ ion from the interstitial to the intracellular compartment).

From a pathophysiologic perspective, the heightened interest in diffusion-weighted imaging stems from the fact that ischemia-induced alterations of water diffusion appear to be a necessary (although not sufficient) antecedent of later-occurring structural changes that signify completed infarction. Thus, the regression of diffusion-weighted hyperintensity can safely be interpreted as evidence of reversibility of an ischemic lesion. Conversely, those factors that contribute to the evolution of an ischemic focus are reflected in diffusion-weighted abnormalities. Notably, ischemic depolarizations (which, as reviewed above, promote the growth of an ischemic infarct) are accompanied by transient increases in hyperintensity on diffusion-weighted images (78). Transient ADC changes propagating bidirectionally have been described within minutes of MCA occlusion in rats (79, 80), consistent with spreading depolarizations.

Promising strategies for metabolic neuroprotection in cerebral ischemia*

Antagonism of excitatory amino acids (84)
N-methyl-D-aspartate (NMDA) antagonists (85)
Noncompetitive (86)
Competitive (87)
Glycine-site (88)
Non-NMDA (AMPA) antagonists (89, 90)
Agents affecting nonglutamatergic neurotransmission
Adenosine agonists (91)
Therapeutic hypothermia (92)
Calcium-channel antagonism
Voltage-sensitive calcium channel antagonists (93)
N-channel blockers (94)
Sodium-channel antagonism/blockade of glutamate release (95, 96)
Antagonism of free radicals (97)
Superoxide dismutase, catalase (98)
21-aminosteroids (99)
Spin-trap agents (100)
Agents affecting nitric oxide (101)
Inhibition of cytoskeletal (spectrin) proteolysis (102)
Antagonism of neutrophil activation or binding
Anti-CD11b or -CD18 monoclonal antibody (103)
Immunosuppressive agents (104)
Cytokine receptor antagonists (105)
Neurotrophic factors
Basis fibroblast growth factor (106)
Combinations of neuroprotectants (107)

* Literature citations are to representative, positive experimental studies or review articles.

The Multiplicity of Ischemia Mechanisms: A Cause for Therapeutic Optimism

That there are multiple potential avenues of neuroprotection in cerebral ischemia should come as no surprise in view of an extensive and ever-widening body of experimental literature that convincingly establishes that ischemic injury can be reduced by targeting several diverse but mutually interactive mechanisms which contribute to its genesis. The Table, which summarizes many of these avenues, is intended merely to provide representative examples of adequately controlled recent studies (largely, of focal cerebral ischemia) from the experimental literature that support therapeutic efficacy.

As is evident from the scientific program of this year's International Joint Conference on Stroke and Cerebral Circulation (Anaheim, Calif, February 1997) and from a recent review (81), clinical trials are currently in progress for each of the following pharmaceutical classes: anticoagulants (warfarin, heparinoids), thrombolytic agents (urokinase, alteplase), fibrinogen-depleting agents (Ancrod), antiplatelet agents (aspirin, clopidogrel), glutamate receptor or channel blockers (eg, CNS 1102, remacemide), glycine-site antagonists (eg, ACEA 1021), calcium channel blocker (very early use of nimodipine), voltage-gated channel blockers (eg, lubeluzole, riluzole, fosphenytoin), oxygen radical scavengers (high-dose tirilazad), blockers of neutrophil adhesion (anti-ICAM-1), neurotrophic factors (basic fibroblast growth factor), and phospholipid precursor (citicoline).

Adding to the sense of optimism generated by this plethora of experimental and clinical activity in the field of ischemic neuroprotection is the growing realization that there is a *commonality of injury mechanisms* shared by cerebral ischemia, neural trauma, and even degenerative neurologic disorders. Hence, therapies efficacious for ischemia could ameliorate traumatic brain injury as well (82).

The recognition that ischemic stroke is amenable to therapy if rapidly instituted has given rise to a national "brain attack" initiative, designed to heighten the awareness of physicians, paramedical personnel, and patients alike that acute ischemic stroke must be regarded as a medical emergency requiring very rapid implementation of diagnostic and therapeutic measures (83). Within the next several years, it is expected that positive outcomes will emerge from some of the clinical trials currently in progress; additional therapies will be established for routine clinical application in acute ischemic stroke, and the morbidity of this common condition, once regarded as hopeless, will steadily recede.

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