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Brain Ischemia Research: from Benchside to Bedside

■ The status of stroke care in the 1990s has been somewhat similar to that of the management of myocardial infarction in the 1950s, when the latter was not regarded as an emergency. Stroke needs to be considered an emergency, with patients brought for medical help immediately, and therapy geared toward minimizing brain damage from ischemia started without delay. Although the incidence of stroke has declined in the past decades in the industrialized world, mainly due to better management of risk factors, treatment of stroke is still evolving. Experimental research has made impressive strides in understanding mechanisms involved in ischemic brain injury, and opened avenues to new therapeutic strategies targeted at reestablishing blood flow and limiting the extent of tissue necrosis. Clinical trials are in progress testing newer agents; for example, antioxidant agents, glutamate antagonists, anti-inflammatory agents, anticoagulants, and thrombolytic drugs, to name a few. The most important stride has been the early administration of rTPA (tissue plasminogen activator).

The improvements noted in experimental studies of focal brain ischemia focus on the prevention of pathological processes affecting brain regions surrounding the ischemic core, namely, regions in which blood flow and oxygenation are not critically diminished. These regions, referred to as penumbra, are functionally impaired but structurally intact, and are therefore salvageable. A number of pathological changes occurring at the molecular level have been characterized in the penumbra in the past few years. The purpose of this paper is to discuss the possible therapeutic impact of recent research. ■

Keywords: Brain Ischemia, Mechanisms, Management of Stroke

Types of Ischemia

Generalized or global ischemia of the brain follows cardiac arrest and resuscitation, systemic circulation collapse, or near-drowning. Reduction of cerebral blood flow (CBF) below 35–40% of the normal level leads to a lack of electrocorticographic response. Further lowering of the CBF results in the anoxic depolarization of neurons, which progresses to neuronal necrosis (Powers, 1992). Neuronal death occurs in selectively vulnerable regions of the brain, while glial cells and vascular endothelium are usually spared. The CA1 region of the hippocampus is the most susceptible region in both animal models (Kirino, 1982) and humans (Petito et al., 1987). Neocortical neurons in layers 3, 5, and 6, neurons in caudate and putamen, and Purkinje cells of the cerebellum are other susceptible neurons (Kirino, 1982).

Focal ischemia, on the other hand, follows the thrombotic or embolic occlusion of major cerebral blood vessels, and results in pannecrosis of cells, namely, neurons, glia, endothelium in the infarct area (Kiessling and Hossmann, 1994). A CBF below 15–20% of control for 3–4 hours results in infarction. Laboratory research indicates that therapeutic approaches to obtain reperfusion must be in place within the first 3–4 hours of the onset of ischemia (Ginsberg, 1994).

The brain region surrounding the ischemic core, also referred to as the penumbra, has been defined variably. This region does not have the same critical reduction of CBF as the ischemic core, and is structurally intact, and is therefore potentially salvageable. However, it is a dynamic region that continues to evolve over time, and a number of molecular-level changes have been described in this area in recent years. Recent research has focused on approaches to limit the extent of cellular damage in the penumbra (Kiessling and Hossmann, 1994; Ginsberg, 1993). The molecular mechanisms involved in neuronal cell death in focal ischemia and the therapeutic strategies to protect this potentially viable region are discussed here.

Mechanisms of Ischemic Neuronal Damage

Cerebral ischemia results in a number of hemodynamic, biochemical, and neurophysiologic alterations that can be linked to clinical, behavioral, and pathologic disturbances (Hara Sukamoto, and Kogure, 1993; Siesjo and Siesjo, 1996). There are multiple animal models of brain ischemia that

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have been employed extensively to study mechanisms involved in ischemic brain damage (Ginsberg and Busto, 1989) and to evaluate the efficacy of potential pharmacologic agents. Various mechanisms have been postulated, and it has been suggested that multiple factors are involved in ischemic neuronal death. It appears that there is a cascade phenomenon whereby certain factors play major roles as initiators, and then other factors follow, eventually resulting in neuronal necrosis (Hara et al., 1993; Schurr and Rigor, 1992).

Four major mechanisms implicated in ischemic neuronal damage are: excitatory amino acid neurotransmitter toxicity (Benveniste, 1991; Rothman, 1992), calcium overload (Auer, 1993), formation of free radicals (Siesjo, Agardh, and Bengtsson, 1989), and lactic acidosis (Hakim, 1989). Other possible mechanisms include: endothelium activation, platelet activation, factors released from white blood cells, cytokines, abnormalities in hemostasis, factors associated with repair, and altered gene expression. Several studies using experimental models have revealed the expression of a number of genes in the ischemic brain (Morgan and Curran, 1995; Nowak, 1990). These may be immediate/early genes (of the c-fos, c-jun family), intermediate genes (heat shock proteins), or late genes (trophic factors). Intracellular signal-transduction mechanisms are activated by ischemia, and these in turn modify the mechanisms of expression of genetic information.

An understanding of the various mechanisms forms the basis for the development of therapeutic strategies for stroke treatment. Below, we discuss accepted as well as potential modalities for stroke management.

Management of Stroke

General Strategies

Management of acute stroke includes the control of vital signs, prevention of the stroke's progression, and prevention of secondary medical complications (Brott and Reed, 1989). Although there are no specific drugs available as yet to reduce the infarct size, various measures to control risk factors have led to significant improvements in clinical outcome (Shahar, McGovern, and Sprafka, 1995; Bronner et al., 1995). A number of agents intended to either increase the cerebral blood flow or protect brain tissue from further damage are being studied for potential use (Barnett, Eliasziw, and Meldrum 1995a; Barinaga, 1996; Ginsberg, 1995).

Patients with stroke need to be admitted to the hospital as an emergency, preferably within 3 hours of the onset of the stroke (Pessin et al., 1997; Webb et al., 1995). A number of organizations in the U.S., such as the National Institute for Neurological Disease and Stroke, the American Heart Association, and the National Stroke Association, have undertaken public educational campaigns as well as physician awareness programs to regard stroke as an emergency (Pessin et al., 1997). Stabilization of vital signs, airway support, management of cerebral edema, and management of hypertension comprise some of the early management concerns in emergency treatment of a patient with stroke (Futrell and Milikan, 1996). Emergency radiologic imaging by computing tomography (CT) without contrast is recommended to exclude intracerebral hemorrhage (Mohr et al., 1995). The chance of a stroke being hemorrhagic is approximately 20%, and the chance of it being ischemic is 80%. A normal CT scan does not exclude an ischemic stroke, because sometimes the changes may not be seen for up to 48 hours following the onset of the stroke (Mohr et al., 1995).

Recent reports indicate that new technologies of perfusion-weighted and diffusion-weighted magnetic resonance imaging (DWI) show abnormalities rapidly during the first few hours after a stroke (Lovblad et al., 1998; Read et al., 1998; Rordorf et al., 1998). A retrospective analysis of DW-MRI performed on 98 human patients within 6 hours of onset of stroke showed sensitivity of 94% and specificity of 100% (Lovblad et al., 1998). Still further, this technique detected cerebral ischemia 3.75 hours after stroke onset in another study of 9 patients (Read et al., 1998). It is projected that these new imaging technologies will be able to predict final lesion volumes within the first few hours of the onset of stroke, and possibly as early as the patient can be placed in the scanner.

Medical complications are a major cause of death in patients with stroke. An electrocardiogram and other laboratory workup, including a complete blood count, a CPK measurement, and coagulation tests should be performed to manage the coexistent medical conditions (Futrell and Milikan, 1996). Anticoagulants should be considered early. Heparin is useful for short-term anticoagulation to prevent cardiogenic emboli. It is contraindicated in large embolic strokes, hemorrhagic strokes, and severe hypertension (Barinaga, 1996).

Thrombolytic Agents

A number of clinical trials of intravenous (i.v.) thrombolysis have been conducted with the hope that recanalization of an occluded vessel may be achieved and the infarct size reduced. The results of these trials have varied, probably due to differences in the drugs used, the time interval from the onset of stroke to treatment, the severity of the lesion, the vessel involved, etc. The administration of r-TPA (tissue plasminogen activator) in a European trial

showed benefit only in a subset of patients studied, while an American trial was more positive. The study conducted by the National Institute of Neurological Disorders and Stroke (NINDS) found that i.v. r-TPA significantly improved stroke outcome in carefully selected patients treated with the agent within 3 hours of the onset of stroke (Adams et al., 1994; 1996). These outcomes were studied after 3 months of stroke. The U.S. Food and Drug Administration approved the drug for stroke patients in June 1996. This drug should only be used in the nonhemorrhagic type of stroke, and it must be given very early after the onset of the stroke. The risk of hemorrhage increases further if the thrombolytic agents are given more than 3 hours after the onset of the stroke (del Zoppo et al., 1992).

Other Potential Agents

Other potential agents being studied presently include neuroprotective agents such as calcium channel blockers (Auer, 1993), free-radical scavengers (Siesjo, Agardh, and Bengtsson 1989; Rice-Evans and Diplock, 1993), glutamate antagonists (Graham et al., 1993; Scatton et al., 1991) and anti-inflammatory agents (Kochanek and Hallenbeck, 1992; Chen et al., 1994).

Calcium Channel Antagonists

It is well established that an increase in intracellular calcium plays a significant role in mediating pathogenesis of ischemic neuronal injury (Auer, 1993; Dienel, 1984). However, the results of many experimental studies using calcium channel blocking agents in both focal and global ischemia have been mixed (Auer, 1993). In contrast to primary ischemia, calcium channel blockers have been shown to reduce cerebral infarction and improve the outcome of secondary ischemia following subarachnoid hemorrhage in a clinical trial (Robinson and Teasdale, 1990; Pickard et al., 1989). Nimodipine (a dihydro-pyridine L-channel blocker) now comprises part of the standard clinical management of patients with acute subarachnoid hemorrhage (Futrell and Milikan, 1996). It is not clear whether the protective action of nimodipine is due to an improvement in cerebral blood flow or some other metabolic neuroprotective action.

Antagonism of Excitatory Amino Acid Neurotoxicity

Glutamate is an excitatory amino acid released in damaged tissue following ischemia (Rothman, 1992). Glutamate antagonists and agents inhibiting glutamate synthesis have been shown to be neuroprotective in animal models (Kaku, Giffard, and Choi, 1993; Wahlestedt et al., 1993). The most extensively studied agent is MK 801, a potent anticonvulsant that binds to NMDA (N-methyl D aspartate) receptors. Initial studies of the use of MK 801 in animal models of transient forebrain ischemia reported it to be neuroprotective (Gill, Foster, and Woodruff, 1988). However, subsequent studies appeared to be contradictory (Buchan and Pulsinelli, 1990). It was felt that the accompanying hypothermia, and not MK 801, was responsible for the neuroprotection. Although MK 801 is of questionable significance in global ischemia, it is markedly effective in focal ischemia models (Ozyurt et al., 1988; Park et al., 1988). Although clinical trials of first-generation NMDA antagonists such as selfotel and eliprodil have failed (Davis et al., 1997), trials with newer agents are under way (Lees, 1997).

Sodium Channel Antagonists and Glycine Antagonists

Agents that inhibit presynaptic release of glutamate by antagonism of presynaptic sodium channels have been found to be useful in experimental stroke. Clinical trials of a number of agents, for example, antiepileptic drugs, phenytoin, and fos-phenytoin, are under way.

Free-Radical Scavengers

Free radicals are molecular species containing only a single electron in the outer orbit. These radicals are highly reactive, and are capable of damaging cell membranes and injuring DNA. The production of free radicals is increased in various types of metabolic disturbances, including ischemia. Use of antioxidant compounds, for example, 21-amino steroids, has shown neuroprotection in animal models (Fisher, Levine, and Cohen, 1990). Although two large trials of tirilazad mesylate (a 21-amino-steroid lipid peroxidation inhibitor) were prematurely terminated because of possible inefficacy, further trials with higher doses are under way.

Another area that has been studied extensively with regard to free radicals deals with nitric oxide (NO). There are three forms of NO synthase (NOS): endothelial and neuronal forms are constitutive, while macrophages elaborate an inducible form. Studies of NOS inhibition in focal ischemia have shown contradictory results, but it appears that neuronal NO production is injurious, while endothelial NO is protective (Huang et al., 1994).

Anti-Inflammatory Agents

It has been suggested that the products of white blood cells contribute to neuronal damage in focal ischemia by way of free radicals (Kochanek and Hallenbeck, 1992). Anti-ICAM (intracellular adhesion molecules) antibodies are antibodies reacting against ICAM on WBCs and preventing the adhesion of WBCs to endothelial cells, thereby inhibiting the migration of WBCs into the infarct region. Various adhesion molecules are known to be expressed in the ischemic cortex (Wang and

Feuerstein, 1995). Animal studies appear to show the anti-ICAM antibodies to be effective in reducing the size of the infarct (Zhang et al., 1995). Clinical trials so far have not been successful.

Manipulation of Brain Temperature

Although the concept of hypothermia relating to organ protection has been recognized for a long time, its value in ischemic brain injury has become apparent only in recent years (Ginsberg et al., 1992). Even a slight drop in brain temperature (1–2°C) during ischemia may lead to histopathologic improvement (Chopp et al., 1989). Moderate hypothermia following traumatic brain injury in human beings has been shown to hasten neurologic recovery (Marion et al., 1997). The mechanisms involved in hypothermic ischemia are not clearly understood, but it has been shown that there is inhibition of the release of excitatory amino acids (Illievich et al., 1994). While hypothermia is neuroprotective, hyperthermia is damaging to the injured brain (Ginsberg et al., 1992). Therefore, it becomes critical to avoid elevations of brain temperature in patients with stroke or head trauma (Sternau et al., 1991).

Carotid Endarterectomy:

The role of surgery in stroke patients is reviewed by Barnett, Eliasziw, and Meldrum 1995b). Randomized clinical trials indicate that the risk of stroke is reduced by carotid endarterectomy in symptomatic patients with at least 70% stenosis. Whether surgery is beneficial for patients who are asymptomatic or have moderate stenosis is not clear.

Trophic Factors

The neurotrophic growth factors, such as nerve growth factors (NGF), brain-derived neurotrophic factor (BDNF), and neurotrophins, are known to play critical roles in CNS development and differentiation. There is evidence now that they may be important in CNS repair after injury (Nikolics et al., 1994). Experimental studies reveal improved neuropathologic outcomes on treatment with NGF (Shigeno et al., 1991) and BDNF (Tsukahara et al., 1994). Growth factors may have potential clinical significance in ameliorating ischemic neuronal injury.

The Integrated approach

It is evident that ischemic neuronal injury is a multifactorial process involving interdigitating mediators (of various cell types) and regulators (Hallenbeck and Frerichs, 1993) with multiple potential causes, and abnormalities of cerebral blood flow. The search for potential therapeutic agents so far has been focused on a select few dominant factors, which vary from time to time and from one study to another. Investigators are now suggesting that it may be time for some novel, unconventional, integrated approaches (Hallenbeck and Frerichs, 1993). Presumably, combinations of thrombolytic and neuroprotective agents will prove to be more effective than either one by itself. It might be possible to administer neuroprotective agents in the early period after the onset of stroke, which might result in extension of the window period for the administration of thrombolytic agents. The addition of other agents (for example, growth factors) at an appropriate time may be another possibility. Other approaches include using a combination of therapeutic agents.

Summary

Stroke is a complex disorder. Improved control of risk factors for stroke has led to considerable progress in reducing the incidence of stroke. Basic science research has increased understanding of the mechanisms involved in ischemic injury, and has opened new avenues aimed toward reestablishing cerebral blood flow and ameliorating neuronal damage. Potential treatment strategies developed in basic science research are now undergoing clinical trials. These include neuroprotective, thrombolytic, and anti-inflammatory agents; antibodies against adhesion molecules on WBCs; and anticoagulants—to name a few. Public awareness that stroke needs to be treated as an emergency, and availability of emergency treatment for stroke patients are necessary. Clinical trials need to have very early patient entry to make use of the "therapeutic window" period within which such treatments are most likely to be effective. Stroke is the most dynamic arena in medicine today, where one can expect to see significant advances in prevention and management of the disorder.

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