SECTION I

INTRODUCTION
CHAPTER 1

Cerebral Ischemia
CEREBRAL ISCHEMIA

Introduction

Cerebral ischemia is a condition in which there is inadequate blood flow to the brain to meet the metabolic demand leading to reduced oxygen supply or cerebral hypoxia and thus causing the death of brain tissue (Fig. 1.1). Ischemic stroke is a sub-type of stroke besides subarachnoid hemorrhage and intracerebral hemorrhage. Of all strokes, 87% are ischemic, 10% are intracerebral hemorrhages and 3% are subarachnoid hemorrhages. According to WHO, stroke was the second commonest cause of worldwide mortality and, the third commonest cause of mortality in developed countries [1-5].

Fig. 1.1. The ischemic cascade leading to cell death.
Therapeutic Strategies For Ischemic Stroke

In treating acute ischemic stroke, two primary strategies are followed: 1) limiting the ischemic insult by early reperfusion and 2) interfering with the pathobiochemical cascade leading to ischemic neuronal damage. In developing an effective therapy, one must also weigh the deleterious consequences of reperfusion injury versus the effects of delay in resuming blood supply to the brain [6]. Within an hour of ischemia, two layers of cerebrovascular tissue develop: the inner core displaying necrosis of both neuronal as well as supporting glial elements, and the outer layer of less severe ischemia called the ischemic penumbra. The cells within the ischemic penumbra can be recovered if timely therapeutic intervention is administered. The size of the ischemic penumbra (portion of the brain that can be rescued) diminishes with time, as the infarct core progressively becomes hypoperfused tissue that cannot be rescued following reperfusion. Ischemic damage in the penumbra, however, is reversible and is the target of rescue via re-establishing blood flow [7].

Reperfusion Therapies

Thrombolytic Agents

The critical time period during which this volume of brain tissue is at risk is referred to as the “window of opportunity”. At present, intravenous administration of tissue plasminogen activator (t-PA) within 3 h of symptom onset is the only US FDA-approved treatment available to re-establish cerebral
blood flow. Early reperfusion with t-PA increases recovery from stroke symptoms by ~30%, with a low rate of serious complications. This will not only rescue neuronal and glial cells within the penumbra, but also glial cells from the central ischemic core zone, thereby limiting the size of infarcted tissue [8]. However, despite the beneficial outcome of early reperfusion, only 3%–8.5% of eligible stroke patients receive t-PA because of the possibility of intracranial hemorrhage [9]. The American Heart Association recently suggested that selected patients may benefit from t-PA up to 4.5 h after stroke, but some counter that the risk of hemorrhagic complications beyond 3 h following ischemia is significantly greater due to breakdown of the BBB [10]. In addition, the increase in cerebrovascular permeability results in diffusion of t-PA to the brain parenchyma [11], causing neurotoxicity [12].

To extend treatment availability to patients with stroke and to reduce the potential for intracranial hemorrhage, intraarterial thrombolysis is a viable option for those who present for medical treatment with in the 3–6 h time window [13]. The strategy behind intraarterial administration is rapid local delivery of a thrombolytic agent through a micro catheter placed near the site of occlusion. This leads to improved recanalization and reduced hemorrhagic complications due to lower doses of thrombolytic agent required to resume blood flow [14]. The disadvantages include the relative complexity of the procedure, delays in initiation of treatment, required technical expertise, and the invasiveness of the procedure [15]. To address the above issues, particularly to compensate for the delay in receiving the treatment, a
combination therapy of intravenous and intraarterial thrombolysis has been tested. The recanalization with IV injection of t-PA is followed by complete recanalization via intraarterial delivery [16].

**Mechanical Thrombectomy**

When thrombolysis is ineffective or is not considered as a viable option, mechanical devices are used to recanalize the occluded cerebral vessel to restore the blood flow [17]. One such device, the Merci Retriever™ (Concentric Medical, Mountain View, CA), consists of a flexible corkscrew-shaped tapered nitinol wire with 5 helical loops that can be threaded in the thrombus, which is then removed by traction [18]. The first prospective study that examined a device-based treatment option for ischemic stroke showed a 43% recanalization rate with the device alone and a 64% recanalization rate with additional intraarterial administration of t-PA [19]. The Catch System™ (BALT Extrusion, Montmorency, France) is a tiny wire basket that retrieves the thrombus [20]. Another useful new technique has been developed in which the clot is simultaneously aspirated from the vessel as it is being extracted. The Phenox Clot Retriever™ (Phenox, Bochum, Germany) consists of a highly flexible core wire compound resembling a pipe cleaner with perpendicularly oriented polyamide microfilaments that create an attenuated palisade. It is deployed distal to the clot and is slowly pulled back under continuous aspiration via the guiding catheter.

The BONnet™ (Phenox, Bochum, Germany) consists of a self-expanding nitinol braiding with polyamide filaments passing through the
interior to enlarge the surface area and enable better fixation of the thrombus mass [21]. The Penumbra System™ (Penumbra, Alameda, CA) has been FDA-approved as a dual approach to clot extraction using aspiration and debulking of the thrombus to reduce or eliminate the clot burden [22, 23]. The system includes reperfusion microcatheters that are connected to an aspiration pump through an aspiration tube. A separator is advanced and retracted within the lumen of the reperfusion catheter to debulk the clot, followed by clot retrieval with a ring device that engages the thrombus by capturing it in clasps with a cylinder that is then withdrawn. The recanalization rate is more then 80% and the device has an excellent safety profile (<3% procedural serious adverse events) [24]. This system has the potential of reopening a vessel without the use of thrombolytics, thus offering dual options for recanalization via a single access platform, and decreases the need to blindly penetrate into the occluded vascular segment because it operates from the proximal end of the clot [25].

Percutaneous transluminal angioplasty (PTA) is particularly useful in cases of atherothrombotic disease, in which the residual stenosis may reduce flow sufficiently to lead to rethrombosis [26]. PTA can be used alone or with subsequent thrombolytic therapy for distal embolization. The largest study of angioplasty for acute stroke showed that recanalization was achieved in 63.9% of thrombolytic-only treated patients, versus 91.2% in the combined thrombolytic plus PTA treatment group. Because of the risk of vessel rupture and distal embolization, this technique is generally reserved for patients whose flow cannot be restored by more conservative methods [26]. Interventional
treatment of acute ischemic stroke with self-expanding stents for flow restoration has been shown to be an effective method for achieving recanalization. In a prospective study, Stent-Assisted Recanalization in acute ischemic Stroke, 100% successful recanalization was demonstrated in 20 patients, with only 1 symptomatic hemorrhage. The disadvantage of this approach is the implantation of a permanent prosthesis and the need for continuous antiplatelet therapy [27, 28].

**Surgical Interventions**

Surgical reconstruction of the cervical carotid artery may be indicated in patients with transient ischemic attack but who are otherwise in good neurologic condition. Another option, microsurgical embolectomy of intracranial vessels, is an invasive procedure involving craniotomy, opening the occluded artery to remove the clot, and reperfusion of the affected area. However, because the procedure is performed through the subarachnoid space via a small craniotomy with a minimal skin incision, it is relatively safe. This can be a last therapeutic option for those patients who are ineligible to receive intravenous or intraarterial thrombolysis, or in the case of failed mechanical thrombectomy. Again, there is a restrictive time window of less than 6 hours from stroke onset for the intervention to be effective. Another surgical procedure utilized in ischemic stroke patients is brain decompression. In the case of major vessel occlusion, large cerebral infarct is developed, commonly associated with rapidly progressing malignant cerebral edema [29]. This leads to compromised neuronal metabolism, decreased cerebral perfusion, and
impaired oxygenation. In addition, shifting of intracranial contents and transtentorial herniation, is the leading cause of death in these patients [30]. Because this kind of cerebral edema is refractory, i.e., not amenable to other forms of treatment, brain decompression is considered a therapy of last resort. Decompressive hemicraniectomy with duraplasty is a complex procedure in which a part of the skull vault is removed and the dura is opened to give more room for the expanding brain. Then, a Silastic sheet, watertight Lyodura, or pericranial grafts are placed over the craniectomy for brain protection. This procedure has been shown to result in increased cerebral perfusion, better survival, improved neurological outcomes, and a reduction in the volume of the infarction. Another, more invasive craniotomy involves resection of infarcted tissue and/or uncal resection. Resection of dead tissue makes room for reperfusion of live tissue in the affected area. Both types of procedures appear to yield satisfactory outcome results [31, 32].

**Neuroprotective Therapies**

Thrombolysis is likely an effective therapeutic modality because it helps restore blood flow and improve cellular metabolism in ischemic regions not yet irreversibly injured. However, thrombolysis is not targeted at the cellular consequences of ischemia. Therefore, it is essential to add a component that would act as a neuroprotective or prevent the damage caused by reperfusion injury. In fact, the Stroke Progress Review Group, which is charged with assisting the National Institute of Neurological Disorders and Stroke (NINDS) in addressing the Institute’s Stroke Research Program, has recommended
research on combinations of neuroprotectants or neuroprotectants plus reperfusion therapy. Addition of neuroprotectants would protect neurons, which are susceptible to apoptosis, and could minimize the damage due to reperfusion injury. [33, 34]

**Antioxidant Therapy**

Upon reperfusion, cells are often in a state of oxidative stress, which results in further tissue injury, known as reperfusion injury. ROS are usually scavenged by antioxidant enzymes, primarily superoxide dismutase (SOD), by catalyzing the dismutation reaction of the superoxide anion to hydrogen peroxide (H$_2$O$_2$). Catalase and glutathione peroxidase, on the other hand, protect cells from the toxic effects of H$_2$O$_2$ by catalyzing its decomposition into water [35]. However, two pharmacodynamic factors impede the straightforward use of native forms of antioxidant enzymes in cerebral ischemia. First, their molecular weight is well below the renal glomerular filtration cutoff, resulting in their rapid clearance from systemic circulation (e.g., $t_{1/2}$ of SOD in rats = 4–8 min, catalase = 8–10 min). Second, they are negatively charged at physiologic pH and therefore do not readily cross cell membranes [36]. Transient disruption of BBB permeability might permit some access of exogenous enzymes to ischemic neuronal tissue, but they do not permeate cells; neurons and astrocytes do not appear to take up the native enzyme under normal conditions, and hence cannot neutralize ROS formed intracellularly [37]. Because of these challenges, animal studies have shown no improvement in cerebral blood flow or neurological recovery with SOD or SOD with catalase [38,39].
Anti-Inflammatory Therapy

Cerebral ischemia activates an inflammatory reaction within hours of the injury. Suppression of inflammation using a variety of drugs has been shown to reduce infarct area in animal studies. Commonly used anti-inflammatory agents are aspirin and the lipid-lowering statins. A combination of aspirin and extended release dipyridamole was found to be more efficacious than aspirin alone for nonfatal stroke by the second European Stroke Prevention Study (ESPS-2) and the European/Australian Stoke Prevention in Reversible Ischemia Trial (ESPRIT) [40]. In an investigation of the anti-inflammatory and neuroprotective properties of statins, the Stoke Prevention by Aggressive Reduction in Cholesterol Level study showed that treatment with high-dose atovastatin reduces the risk of stroke in patients with first attack of stroke and no known coronary artery disease [41]. In addition to aspirin and statins, two leukocyte adhesion inhibitors, Enlimomab and LeukArrest, were studied in patients with ischemic stroke. Although Enlimomab was shown to reduce the damage in stroke models, patients who received it experienced significantly more negative effects relative to placebo controls [42].

Hypothermia

Another neuroprotective approach was explored in the “Intravenous Thrombolysis Plus Hypothermia for Acute Treatment of Ischemic Stroke (ICTuS-L)” study of the effects of induced hypothermia and thrombolysis after acute ischemic stroke. Hypothermia is thought to serve a neuroprotective role in stroke via inhibition of the MIP-3α-CCR6 inflammatory pathway [43].
Although hypothermia has been shown to confer some protection against damage in cardiac arrest and neonatal hypoxic-ischemic encephalopathy patients [44, 45], its effectiveness in acute ischemic stroke has not been definitively demonstrated. Negative consequences, including pneumonia, were seen more frequently in patients who had undergone hypothermia treatment, compared to controls in this study. Disappointingly, there was no significant benefit in mRS between the two trial groups [46].

**Other Therapeutic Strategies**

The understanding of various pathogenetic mechanisms of stroke leads to the development of newer therapeutic approaches with different modes of action as well as with a wider therapeutic window. Anti-ischemic agents like glutamate antagonists, anti-apoptotic agents and ion-channel modulators are the currently studied therapeutic interventions for ischemic stroke [47, 48].

**Neuronal Rescue**

Another critical issue in stroke therapy is how to recover areas of infarcted brain that appear irreversibly damaged due to ischemia. To address this issue, research is now focused on understanding neurogenesis, particularly endogenous repair mechanisms such as the involvement of neuronal progenitor cells and their proliferation and differentiation into neural cells [49]. However, use of a small population of endogenous neuronal progenitor cells and their limited capacity to regenerate under inflammatory conditions may not be enough to achieve significant neurological recovery. Therefore, several growth factors (e.g., epidermal, fibroblast, vascular endothelial growth factors and
erythropoietin) have been tested to increase proliferation and migration of progenitor cells. The major challenge seems to be inducing sufficient proliferation to repair the devastating neuronal damage following ischemia, promoting survival of the newly formed cells in the hostile environment, and more importantly, inducing proper connectivity of the newly formed cells with the existing circuitry [49]. An alternative approach is the transplantation of stem cells, but a number of factors could influence the success of this approach, the main one being the survival of the transplanted cells and the likelihood of their proper differentiation into neuronal cells [50, 51].
REFERENCES


