Ischemic Stroke: Basic Pathophysiology and Clinical Implication

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Abstract

Stroke is one of the most frequent causes of death worldwide. Clinically, stroke is a heterogeneous disease. Brain injury after stroke follows diverse signaling cascades that evolve in a complex spatiotemporal pattern. The core of the infarction is characterized by fast necrotic cell death. In the surrounding area, the penumbra, different cascades lead to delayed forms of cell death. However, endogenous protective mechanisms in the brain are geared to counteract the damaging cascades by mediating ischemic tolerance.

Keywords

Anterior cerebral artery syndrome · Apoptosis · Ataxic hemiparesis · Death receptors · Doppler and duplex sonography · Dysarthria-clumsy hand syndrome · Fluid-attenuated inversion recovery (FLAIR) · Ischemic penumbra concept · Ischemic stroke · Lactate-acidosis hypothesis · Lacunar stroke · Middle cerebral artery syndrome · Peri-infarct depolarizations · Posterior cerebral artery syndrome · Pure motor hemiparesis · Pure sensory stroke · Recanalizing therapy · Stroke · Transient ischemic attacks (TIAs)

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Abbreviations

ACA	Anterior cerebral artery
AMPA	α-amino-3-hydroxy-5-methyl-4-isoazolepropionic acid
ASIC	Acid-sensing ion channel
BA	Basilar artery
BBB	Blood–brain barrier
CBF	Cerebral blood flow
CCT	Cranial computed tomography
COX-2	Cyclooxygenase-2
CT	Computed tomography
DSA	Digital subtraction angiography
DWI	Diffusion-weighted imaging
ECG	Electrocardiography
EPO	Erythropoietin
FLAIR	Fluid-attenuated inversion recovery
ICA	Internal carotid artery
IL	Interleukin
MMP	Matrix metalloprotease
MOMP	Mitochondrial outer membrane depolarization
MRI	Magnetic resonance imaging
NMDA	*N*-methyl-d-aspartate
NO	Nitric oxide
NOS	Nitric oxide synthase
PCA	Posterior cerebral artery
PET	Positron emission tomography
PID	Peri-infarct depolarization
PWI	Perfusion-weighted imaging
ROS	Reactive oxygen species
rtPA	Recombinant tissue plasminogen activator
SIDS	Stroke-induced immunodepression
SOD	Superoxide dismutase
TCD	Transcranial Doppler
TGF-β	Transforming growth factor beta
TIA	Transient ischemic attack
TNF-α	Tumor necrosis factor-α
VA	Vertebral artery

Brief History

More than 2400 years ago Hippocrates first described the sudden onset of paralysis – apoplexia, which translates to “struck down by violence” and which was used to describe any kind of sudden death. However, Hippocrates sought the reason for this state in a wrong mixture of the four humors, blood, phlegm, yellow bile, and black

bile. It was not until the mid-seventeenth century that Johann Jakob Wepfer, a Swiss physician, recognized stroke as a vascular disease. He described first evidence that "apoplexia" was caused by intracerebral hemorrhage or occlusion of a cerebral artery. Further important contributions to the understanding of stroke were made by Rudolph Virchow (1821–1902, arterial thrombosis), Carl von Rokitansky (1804–1878, association of stroke with heart disease), Jean-Martin Charcot (1825–1893, anatomical description of brain vasculature, relevance of aneurysms for cerebral hemorrhage), and Otto Binswanger (1852–1929, description of vascular dementia). However, the most important observation and discoveries for our current pathophysiological understanding and clinical approaches in stroke were made in the second half of the twentieth century. Early in the twentieth century, Hans von Chiari (1851–1916) first recognized the connection between carotid artery disease and stroke. James Ramsay Hunt (1872–1937) later described clinical cases of hemiplegia, where he identified partial or complete occlusion of the carotid arteries as responsible for these syndromes. In 1951, Charles Miller Fisher (born 1913) published his clinicoanatomical studies on the importance of carotid artery occlusion for stroke pathophysiology. Fisher later demonstrated that thromboembolic mechanisms underlie most ischemic strokes. Consequently, in 1991, a large clinical trial led by Henry J. M. Barnett (born 1922, North American Symptomatic Carotid Endarterectomy Trial, NASCET) demonstrated the benefits of surgical carotid endarterectomy in patients with transient ischemic attacks or minor stroke. Furthermore, several clinical trials demonstrated the safety and efficacy of early thrombolysis using recombinant tissue plasminogen activator (rtPA). Likewise, various antiplatelet agents were demonstrated beneficial in stroke prevention. To date, early revascularization remains the sole effective therapy for stroke.

Introduction

Cerebrovascular disease, including stroke, ranks second as the cause of death worldwide. Roughly 1 in 20 adults is affected by stroke in developed countries, and mortality over the first year after the first stroke is approximately 20%. However, the socioeconomic burden of stroke is not a consequence of mortality but is imposed by the large majority of patients that survive and remain physically or mentally disabled. Comparing trends in stroke incidences between high- and low- to middle-income countries over the past decades shows an alarming divergence. While there is a 42% decrease in stroke incidence in high-income countries, the incidence of ischemic stroke has increased more than 100% in low- to middle-income countries.

Stroke is a heterogeneous group of diseases. Cerebral artery occlusions are the major cause and account for 80–85% of all strokes in the Western world. Primary intracerebral and subarachnoid hemorrhages, as well as sinus thrombosis, have a relatively low incidence and account for the remaining 15–20%. On the contrary, hemorrhagic stroke accounts for up to 50% of all strokes in Asia.

Ischemic stroke is caused by a transient or permanent reduction of blood flow in the territory of a cerebral artery – typically by embolic or thrombotic occlusion.

Embolisms of either arterioarterial or cardiac genesis account for 75% of all cerebral vessel occlusions and are the most frequent cause for focally impeded blood flow within the brain. Embolisms result in damage of a larger territory of the brain, depending on vascular collateralization distal of the occlusion. Thrombotic events typically target small cerebral arteries with mostly lacunar infarcts or subcortical encephalopathies. Microangiopathical causes, such as in situ thromboses and hyalinoses of the arterioles, occur in about 20% of all cases. Hemodynamic infarctions as a result of high-grade stenoses of the cerebral arteries are comparatively rare (less than 5%). In this case, infarcts usually occur in the area between two vascular territories ("watershed zones"). Eventually, an ischemic stroke results in the death and dysfunction of brain cells.

Stroke is primarily a disease caused by vascular occlusion. It is therefore not surprising that the size of the subsequent infarction can be predicted by the severity and duration of the reduction in local cerebral blood flow (CBF). The probability for infarction is higher than 95% if the CBF in the affected tissue area drops below 25% of normal. However, the probability for infarction in areas with CBF values higher than 50% of normal CBF is less than 5%. While these threshold values have primarily been determined in experimental models of stroke, they have been validated in humans by quantitative PET- and MRI-imaging methods. Thus, the initial reduction in CBF determines the size of the infarct. This, however, only holds true under the premise that there is no early therapeutic or spontaneous reperfusion.

Cellular and Molecular Pathophysiology of Stroke

The modern understanding of stroke pathophysiology extends far beyond the immediate effects of the impairment of local blood circulation. Brain damage in stroke is the result of a multitude of highly complex mechanisms, leading to infarct maturation. As the brain has a very high demand for oxygen and glucose, a disruption of circulation primarily leads to a depletion of substrates within minutes. In addition, toxic metabolites accumulate. This leads to an energy deficit in the affected tissue. The result is functional or even structural damage to the cells, depending on the degree and duration of the energy deficit.

The events that take place in the ischemic area are complex and follow a stereotypic temporal and spatial pattern.

Early after the onset of the perfusion deficit, the major mechanisms of damage include *excitotoxicity*, the production of *reactive oxygen/nitrogen species*, *tissue acidosis*, and *peri-infarct depolarizations. Inflammation* and *programmed cell death* (*apoptosis*) ensue. However, in parallel to these destructive cascades, protective mechanisms that lead to the amelioration of the damage are also activated. These mechanisms can be examined in models of *ischemic tolerance*. Furthermore, the *concept of the ischemic penumbra* is essential for understanding these processes and will be described in detail below.

In addition to the *acute* events triggered by the focal perfusion deficit in the brain, aspects of neuronal plasticity and regeneration have emerged as important concepts

on a more *chronic* timescale. The focus of research in these areas is centered around spontaneous and therapeutically induced neuroneogenesis, homing of blood-derived cells into the brain, and their transdifferentiation or fusion with parenchymal cells and consequently cell replacement therapies.

The Concept of the Ischemic Penumbra: Temporal and Spatial Events After Stroke

The concept of the ischemic penumbra was first introduced by Astrup in 1981. In the ischemic brain, two tissue areas can be distinguished – the core of the infarction and the surrounding zone which is called the (ischemic) penumbra. It is now generally accepted that not all brain cells die immediately after an ischemic stroke, but rather that cell death advances in a defined spatial and temporal continuum, in particular in the perilesional penumbra.

Almost immediately after vessel occlusion, the ischemic core is defined where cells are destined to die irrespective of therapeutic interventions unless rapid restoration of blood flow can be achieved. The massive reduction of blood flow in the ischemic core leads to a breakdown of cellular metabolism and energy supply, ion homeostasis, and a consecutive loss of cellular integrity. The result is cell death within minutes: necrosis of cells and tissue evolves.

Collaterals provide residual circulation in the surrounding penumbra. This tissue is functionally silent albeit metabolically still active and therefore salvageable. However, the disruption of cellular homeostasis in the penumbra leads to slow cell death and a step-by-step growth of the lesion, and the previously viable brain becomes infarcted tissue. In the penumbra, apoptotic and inflammatory signaling cascades play an important role. Early after the onset of a stroke, the penumbra can account for up to 50% of the volume that later becomes infarcted (Fig. 1).

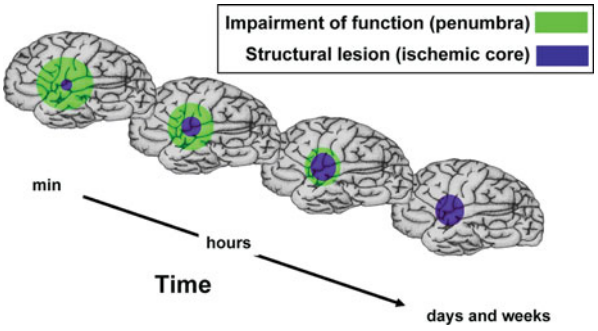

Fig. 1 *The ischemic penumbra*. The ischemic core, a region where cerebral blood flow (CBF), is reduced below a critical threshold in which cell death and structural damage are inevitable and are surrounded by the penumbra. In the penumbra, residual CBF prevails, and cells are functionally impaired but viable. From the onset of the perfusion deficit, both core and penumbra are dynamic in space and time, which can result in the growth of the core at the cost of the penumbra if sufficient (reperfusion) therapy is not initiated (Reproduced with permission from Dirnagl et al. 1999)

Damage of the Blood–Brain Barrier

The integrity of the blood–brain barrier (BBB) depends on an intact cellular matrix, which is composed of endothelial cells and astrocytes. After cerebral ischemia, the cellular matrix, intercellular interactions, and signal transduction are damaged. Proteases such as matrix metalloproteases (MMPs) are involved in mediating damage to the BBB. MMP2 and MMP9 are induced 1–3 h after cerebral ischemia. Expression levels of MMPs correlate with the severity of the damage of the BBB, the risk of hemorrhagic transformation of the stroke, and the extent of neuronal damage. Destruction of the basal lamina by the MMPs is one of the prerequisites for leucocyte immigration after stroke and leads to vasogenic edema. Genetic as well as pharmacologic inhibition of MMPs not only reduces the damage to the BBB but also reduces infarct volume.

Mechanisms of Cell Death in Stroke

Although the exact timing and cellular pathways are incompletely understood, it is generally accepted that mechanisms actively promoting cell death are triggered after stroke. The cellular pathways ultimately leading to cell death are necrosis, which is characterized by ischemic or edematous cell changes; apoptosis with a number of morphological (e.g., apoptotic bodies), biochemical (e.g., DNA laddering), pharmacological, and molecular characteristics (e.g., activation of caspases); or autophagocytosis.

Initially, ischemic injury is induced by energy failure, an increase of intracellular calcium, and release of excitatory amino acids with subsequent excitotoxicity. This activates downstream mediators of ischemic damage including free radical and peroxynitrite production, calpain, phospholipases, and poly-ADP-ribose polymerase activation. Concomitantly, apoptotic pathways are initiated. Peri-infarct depolarization waves further compromise the energy balance of ischemic neurons in the penumbra. In addition, inflammation contributes to the progression of tissue damage. Secondary stages of cell death may involve long-term changes in macromolecules and other key metabolites. All of these events are potential targets for therapeutic intervention (Fig. 2). In the following, the key events are addressed in more detail.

Peri-infarct Depolarization

Anoxic depolarizations in the core of the infarct are caused by oxygen depletion in neurons and nonneuronal cells and the subsequent release of glutamate, other excitatory amino acids, as well as potassium. Cells thereby remain depolarized and go on to die. In the penumbra, cells may repolarize at the cost of high energy expenditure. Following depolarization, the release of neurotransmitters and potassium into the extracellular space initiates repetitive waves of so-called peri-infarct depolarizations (PIDs). Typically, PIDs originate from the core of the lesion and propagate to the periphery in a wavelike fashion for at least 6–8 h at a frequency of 1–4 events per hour. Thereby, a wave of depolarizations propagates away from the ischemic core. Several lines of evidence from ischemic animal models as well as from human studies prove that PIDs in fact contribute to tissue damage after stroke. The total number and frequency of PIDs correlate with the final lesion volume and

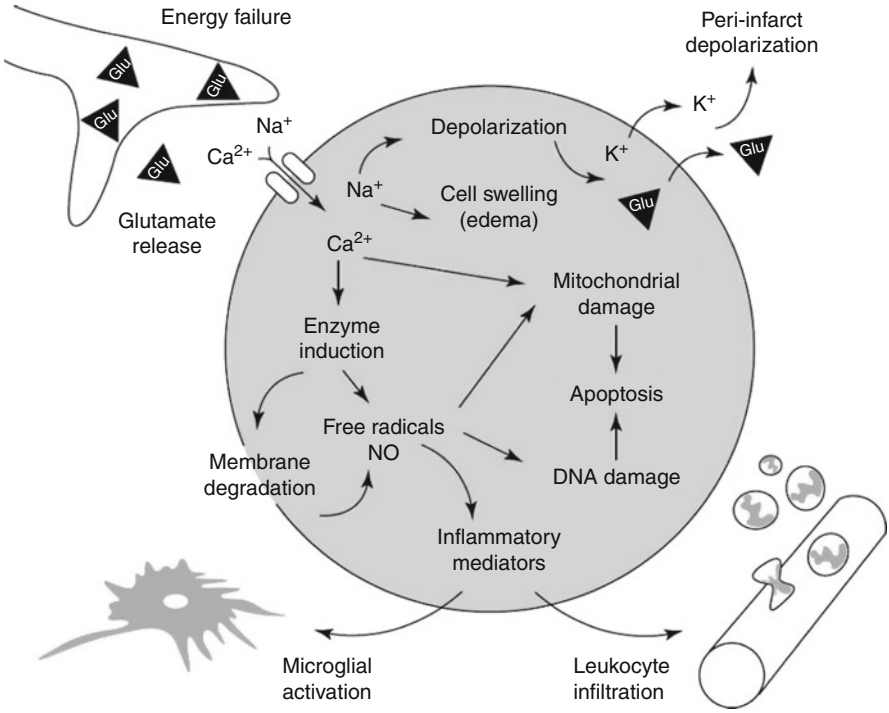

Fig. 2 *Simplified overview of pathophysiological mechanisms in the focally ischemic brain*. Energy failure leads to depolarization of neurons. Activation of specific glutamate receptors dramatically increases intracellular levels of calcium (Ca^{2+}), sodium (Na^{+}), and chloride (Cl^{-}) while potassium (K^{+}) is released into the extracellular space. Diffusion of glutamate (*Glu*) and potassium in the extracellular space can propagate a series of spreading waves of depolarization (peri-infarct depolarizations). Water shifts to the intracellular space via osmotic gradients and cells swell (edema). The universal intracellular messenger calcium activates a number of enzymes such as proteases, lipases, endonucleases, etc. Free radicals and nitric oxide (*NO*) are generated which in turn damage membranes, mitochondria, and also DNA itself, all of which may trigger apoptosis by intrinsic mechanisms. Inflammatory mediators are released to attract and activate immunocompetent cells such as microglia and blood-borne inflammatory cells (Reproduced with permission from Dirnagl et al. 1999)

cellular damage, and it has been shown that the propagation of each depolarization contributes to the immediate growth of the ischemic lesion from the core to the periphery. Furthermore, therapeutic interventions aimed at reducing PIDs (such as NMDA or AMPA receptor blockade) salvage tissue. Subsequent repolarization, an energy-dependent process, can further contribute to the growth of the ischemic lesion, lethally damaging metabolically comprised cells in the penumbra.

Excitotoxicity

After focal ischemia, the brain parenchyma suffers from a profound loss of oxygen and glucose, the brain's major sources of energy generated by oxidative phosphorylation. The subsequent local energy deficit induces depolarization of neurons and

glia, resulting in activation of voltage-gated calcium channels and the release of excitotoxic amino acids into the extracellular matrix. In particular, the release of glutamate undergoes a rapid presynaptic or astrocytic reuptake under physiological conditions. However, after binding to and thereby activating ionotropic *N*-methyl-d-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoazolepropionic acid (AMPA) receptors, glutamate promotes excessive direct and indirect calcium influx into neurons. Increased intracellular calcium acts as a universal second and third messenger to trigger an array of downstream phospholipases and proteases that degrade membranes and proteins essential for cellular integrity. Furthermore, mitochondrial outer membrane depolarization (MOMP) and subsequent cell death are triggered by intracellular calcium overload. Additionally, sodium and chloride enter neurons via channels for monovalent ions (e.g., the AMPA receptor), passively followed by water, causing intracellular ("cytotoxic") edema. Substantial imbalances of other ions include large amounts of zinc that are stored in vesicles of excitatory neurons which are released upon depolarization and contribute to excitotoxic cell death. Finally, excitotoxicity may be an initiator of molecular events that lead to apoptosis and inflammation (see below) in regions where rapid necrosis does not occur.

Oxidative and Nitrosative Stress

In consequence of ischemia, and particularly after reperfusion, reactive oxygen species (ROS) such as superoxide, hydrogen peroxide, and hydroxyl radical are generated. ROS are also key mediators of tissue damage in other organs such as the heart or kidneys suffering from reperfusion injury. Free radicals react with virtually any cellular component (carbohydrates, amino acids, DNA, and phospholipids) and cause direct structural damage. Additionally, free radicals trigger a vicious cycle in the mitochondria, inhibiting the electron transport chain which leads to excess superoxide production and activation of mitochondrial permeability transition (mPT) and induction of MOMP. Besides impeding the production of ATP through loss of mitochondrial potential, mPT leads to mitochondrial swelling and the release of proapoptotic molecules. Oxidative stress is closely linked to excitotoxicity, energy loss, and ionic imbalances, and all of these events further contribute to tissue damage. Endogenous ROS scavengers such as superoxide dismutase (SOD) or glutathione mitigate injury induced by oxidative stress but are insufficient to counteract damage evoked by focal ischemia. Mice overexpressing SOD have shown reduced injury following focal occlusion, supporting interventions aimed at enhancing endogenous ROS scavenging mechanisms as therapeutic targets after ischemic stroke. Furthermore, cyclooxygenase-2 (COX-2) is an important mediator of oxidative damage. Both genetic and pharmacological inhibitions of COX-2, which are mostly expressed in the penumbra and lead to the production of free oxygen radicals and prostanoids, reduce tissue damage experimental stroke.

In addition to oxidative stress, nitrosative stress also contributes to tissue damage. Nitric oxide (NO) itself can be both beneficial and deleterious during brain ischemia, depending on the time and place of its production. NO is synthesized from l-arginine by several isoforms of NO synthase (i.e., NOS I, NOS II, and NOS III). Under

conditions of increased oxidative stress, NO reacts with superoxide anions to generate the highly reactive and cytotoxic peroxynitrite. In models of focal cerebral ischemia, inhibition of inducible NO synthase (iNOS) confers favorable outcomes even if treatment is started 24 h after induction of ischemia. Compared to the constitutively expressed isoforms of NO synthase, eNOS, and nNOS, iNOS produces greater amounts of cytotoxic NO. As blockade of both iNOS and COX-2 is still effective to prevent damage after delayed treatment (6–24 h after onset of ischemia) in rodent models of stroke, these two enzymes present interesting targets for novel therapeutic strategies.

Tissue Acidosis

Ischemia-induced acidosis is an important mediator of damage in the context of focal cerebral ischemia. While acid-sensing ion channels (ASICs) have been demonstrated to contribute to acidotic damage in cerebral ischemia, the mechanisms leading to acidosis are still far from clear. For many years, it has been advocated that acidosis in cerebral ischemia is triggered through the accumulation of lactate. Under hypoxia, anaerobic glycolysis is induced and thereby lactate production. The "lactate-acidosis hypothesis " is frequently attributed to explain the glucose "paradox" of cerebral ischemia. The "paradox" is that there is experimental evidence that high glucose levels increase tissue damage, despite the importance of glucose for neuronal energy production. Tissue acidosis interferes with intracellular protein synthesis and leads to the generation of different species of free oxygen radicals, thereby increasing tissue damage. However, the role of acidosis in stroke pathophysiology is complex and incompletely understood, and the lactate-acidosis hypothesis has also been questioned. In particular, acidosis can block NMDA receptors, thereby mediating antiexcitotoxicity. Furthermore, it has been argued that the reported negative effects of induced hyperglycemia in stroke models are an experimental artifact, resulting from the massive release of glucocorticoids after glucose infusion.

Apoptosis

Programmed cell death, i.e., apoptosis, relies on the initiation of a cascade of events that are triggered in response to acute damage to the CNS such as ischemic injury. While neuronal and glial cells in the ischemic core of the infarction mostly undergo rapid necrotic cell death within minutes or hours, apoptosis occurs predominantly in the penumbral region, starts hours after the onset of ischemia, and can last for days. Apoptosis is characterized by the initiation of biochemical cascades, leading to the activation of caspases. Caspases are proteases that catalyze the destruction of the cell, its compartments, and molecules. Although bona fide morphological criteria for apoptosis (e.g., using electron microscopy) frequently have not been found in experimental stroke studies, a number of molecular, biochemical, and pharmacological criteria for defining apoptotic cell death are fulfilled in ischemic neuronal death. In addition, apoptosis is an important regulator in the development of the nervous system. For the most part, induction and regulation of apoptosis in the brain relies on mechanisms that are not distinct from other tissues. In general, both caspase-dependent and caspase-independent mechanisms have been described. Caspases

are aspartate-specific cysteine proteases constitutively expressed in the brain, including neurons, and are activated by intrinsic and extrinsic stimuli. Two pathways, the extrinsic and the intrinsic pathways, regulate apoptotic cell death and ultimately result in the disintegration of the cell. The extrinsic pathway includes the activation of surface receptors, so-called death receptors, such as TNF-R (tumor necrosis factor receptor), CD95/Fas, and DR4/5 triggered by TNF, FasL (Fas ligand), and Apo2l/TRAIL (TNF-related apoptosis-inducing ligand), respectively. Subsequently, a cytoplasmic death-inducing signaling complex (DISC) is assembled. Intrinsic activators of apoptosis in the context of ischemia are, for example, elevated intracellular levels of calcium, ROS, glutamate, and DNA damage. By damaging mitochondrial membranes, both pathways directly or indirectly lead to the activation of caspases. Once activated, caspases cleave a number of downstream substrates that include other ("executioner") caspases, DNA repair enzymes such as PARP, cytoskeletal proteins, presenilin, huntingtin, and caspase-activated deoxyribonuclease (ICAD). The most important executioner caspase in the brain is capase-3, which is activated early after ischemia and particularly in the peri-infarct region. Inhibition of caspases, for example, using small oligopeptides that mimic the cleavage site of a caspase substrate reduces lesion size in experimental stroke, and genetic disruption or a pharmacological blockade of caspases shows a robust neuroprotective effect in stroke models. Furthermore, cytochrome c plays an important role in the induction of apoptosis. Once released from mitochondria, cytochrome c induces the formation of the "apoptosome" complex, which further contains the cytosolic protein Apaf-1 and procaspase-9. The apoptosome activates caspase-9, leading to sequential activation of the downstream caspases-20. The release of cytochrome c from mitochondria depends on the integrity of the mitochondrial outer membrane, which is also regulated by the Bcl-2 family of proteins. This family is divided into proteins with pro- (e.g., Bid, Bax, Bak, Bad) and antiapoptotic (e.g., Bcl-2, Bcl-xL) function and regulates MOMP in an ordered series of events or inhibits membrane permeabilization by competition between anti- and proapoptotic family members. Downstream markers of apoptosis include the appearance of terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick-end labeled (TUNEL) cells or phosphatidylserine translocation to the outside of the cell membrane (visualized by annexin V staining) and biochemical evidence of oligonucleosomal DNA fragmentation ("DNA laddering"), as reported in stroke models. An in-depth description of the ordered cascades of events and complex mechanisms ultimately resulting in apoptosis is beyond the scope of this chapter, and the reader is encouraged to explore the literature and the references cited therein.

Inflammation and Cellular Mechanisms

A few hours after the onset of ischemia, the early stage of inflammation starts. It is characterized by the expression of adhesion molecules at the vascular endothelium as well as by circulating leukocytes. Successively, leukocytes adhere to the endothelium and transmigrate from the blood into the brain parenchyma. The interaction between the endothelium and circulating leukocytes is critical for stroke-induced brain inflammation. Within a few hours after the onset of ischemia, endothelial cells express adhesion molecules (e.g., ICAM-1 or VCAM-1) which mediate interaction

with leukocytes. An additional disruption of microcirculation is induced by the accumulation of neutrophil granulocytes cerebral microvessels in the penumbra. The pathophysiological importance of these events has been demonstrated in a variety of experimental settings. Inhibition of adherence of immune cells to the endothelium through the blockade with antibodies against CD18, CD11b, ICAM-1, or VLA-4 ($\alpha 4\beta 1$) or as well as genetic deletion of adhesion molecules reduced accumulation of leukocytes as well as infarct sizes. Furthermore, postischemic inflammation in the brain is aggravated by the production of cytokines and chemokines by activated immune cells (granulocytes, monocytes/macrophages, lymphocytes) as well as neurons, astrocytes, and microglia. In particular, pro-inflammatory cytokines such as TNFα, IL-1, and IL-6 play important roles as mediators of inflammation after cerebral ischemia. Ischemic damage can be reduced by several cytokine (receptor) antagonists such as inhibiting TNFα by TNF-binding proteins. However, genetic deletion of the TNFα-receptor 2 (TNFR2) or IL-6 does not lead to decreased ischemic damage, pointing to a complex involvement of inflammation in cerebral ischemia. In addition to proinflammatory cytokines, anti-inflammatory cytokines such as TGF-β1 and IL-10 are also induced after cerebral ischemia, confining inflammatory aggravation of damage after cerebral ischemia. TGF-β1, a well-known neuroprotectant, seems to play an important role in mediating immunological tolerance after cerebral ischemia. In general, immunogenic proteins induce immunological tolerance mediated by lymphocytic subpopulations expressing TGF-β1. Similar to ischemic tolerance (see below), immunological tolerance mediates protection against otherwise lethal ischemic insults of the brain. In contrast to ischemic tolerance, where protection is only induced for a few days, protection mediated by immunological tolerance can persist for months.

A major role in brain inflammation is ascribed to microglia, the primary immunoeffectors in the CNS. In particular, in the penumbra, microglia is activated after stroke. Activated microglia is able to produce a multitude of proinflammatory cytokines as well as toxic metabolites (especially reactive oxygen species such as peroxynitrite and superoxide) or enzymes (cathepsin). Therefore, inhibition of microglial activation, for example, using the tetracycline antibiotic minocycline is neuroprotective in stroke models.

The relevance of immigration of blood-derived monocytes, which are thought to differentiate into microglia after experimental stroke, however, is under debate. Additionally, astrocytes play an important part in stroke-induced brain inflammation. They produce both proinflammatory cytokines and neuroprotective factors such as erythropoietin, TGF-β1, and metallothionein-2. At present, because of the Janus-faced nature of glia products (destructive, e.g., free radicals, vs. protective, e.g., growth factors), the overall role of cellular inflammation in cerebral ischemia is not clear. Likely, inflammatory cells play different roles at different time points after the ischemic event.

Stroke-Induced Immunodepression (SIDS)

Importantly, cerebral ischemia not only affects the brain parenchyma but also comprises other vital organs, for example, the heart and circulation, or the immune system. Typically, within 3 days after the onset of ischemia, up to 61% of stroke

patients develop a fever. Findings from animal experiments demonstrated that hyperthermia of more than 1 °C does lead not only to dramatically increased levels of the cytotoxic glutamate but also to significantly larger infarcts. Clinical trials demonstrated that morbidity and mortality increase with the occurrence of fever in stroke. The most common cause of fever in the acute course of stroke is an infection, which occurs in 21–65% of stroke patients. Pneumonia is the most frequent infection after stroke, thereby presenting a major risk factor concerning mortality. In contrast, the prevalence of nosocomial (hospital-acquired) infections in general ranges between 4% and 9%. Obviously, risk factors such as immobilization, reduced bulbar reflexes, and drowsiness increase the risk of aspiration-promoted pulmonary infections. However, these risk factors for bacterial infection cannot sufficiently explain why stroke patients have such a high risk of infection. After a stroke, as well as after other insults to the brain, deficiency of the immune system ensues. It has been demonstrated experimentally that severe spontaneous bacterial infections after stroke (mostly pneumonia and sepsis) are the result of immunodepression. After a stroke, overactivation of the sympathetic nervous system is induced, rapidly leading to severe and sustained lymphopenia as well as disturbed lymphocyte and monocyte function. Furthermore, overactivation of the sympathetic nervous system after stroke has also been found in humans. Additionally, severe infections are caused by disturbed secretion of interferon-γ from T cells and NK cells. Cellular reconstitution of the immune system (via adoptive transfer from healthy donors), application of interferon-γ, as well as pharmacological inhibition of the sympathetic nervous system with the β-receptor-blocker propranolol prevented infections. The latter also dramatically decreased the high rate of mortality in a particular mouse model of stroke. Thus, in addition to conventional stroke therapy (see below), approaches to prevent infection after stroke seem to be desirable. Thereby, preventive anti-infective therapy is expected to positively affect a number of negative prognostic factors such as fever, infection-induced arterial hypotension, and the systemic release of proinflammatory cytokines. Additionally, anti-infective treatment with an antibiotic after focal ischemia leads to not only reduced mortality and infarct size but also decreased functional deficit. Thereby, earlier mobilization and rehabilitation seems feasible. A phase IIb clinical trial for preventive antibacterial short-term therapy in patients with acute ischemic media infarction (Preventive ANti-infective THERapy In Stroke; PANTHERIS, Berlin) that was modeled after these experimental findings supported the concept that stroke-induced immunodepression is a serious risk factor for increased rates of infection in stroke patients.

Endogenous Neuroprotection, Ischemic Tolerance, and Conditioning of the Brain

After a stroke, in addition to destructive cascades, endogenous protective mechanisms are activated (Fig. 3). These mechanisms of endogenous neuroprotection and ischemic tolerance have been intensively studied in different models of preconditioning. The principle of preconditioning is to achieve a protected state of a cell, tissue, or a whole organism through a noxious stimulus (trigger), which is applied below but close to the threshold of damage. Such a stimulus induces a

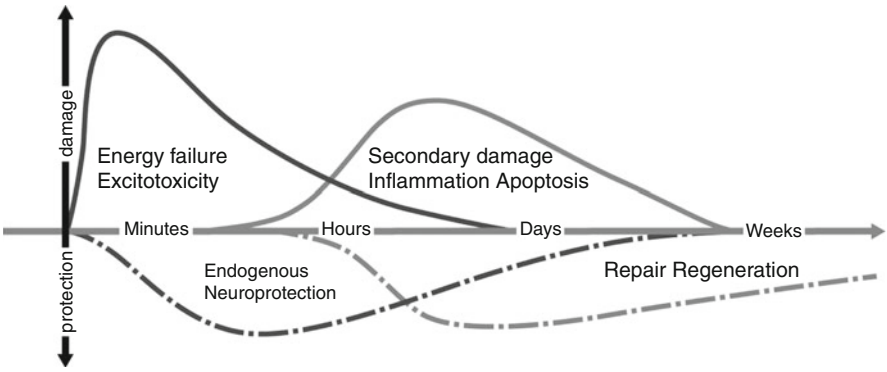

Fig. 3 *Cascades of damaging events and protection in focal brain ischemia*. After the onset of a focal perfusion deficit, neurons and glia are rapidly damaged by excitotoxic mechanisms. Apoptosis and inflammation ensue and further contribute to structural damage. Mechanisms of endogenous neuroprotection are geared to counteract damaging events and can be triggered by conditioning stimuli. Regeneration and repair either elicited spontaneously or after therapy contribute to recovery function in some lesioned areas

protective state against insults otherwise lethal. A large variety of preconditioning stimuli have been found to induce tolerance to ischemia, such as brief ischemia itself ("ischemic tolerance"); hypoxia, reactive oxygen species, inflammation, different types of drugs, and many more can serve as tolerance-inducing stimuli. Furthermore, ischemic tolerance in the brain can also be induced by preconditioning other organs (remote preconditioning). Furthermore, the concept of "conditioning" to induce tolerance to ischemia has been expanded to preconditioning (conditioning stimulus is applied while noxious stimulus, e.g., ischemia, is still present) and post-conditioning (conditioning stimulus is applied shortly after the noxious stimulus). In the case of preconditioning, ischemic tolerance occurs within two time windows after induction. The early window of tolerance exists after about 5–120 min after stimulation (classical preconditioning). Delayed preconditioning occurs after a latency of about 24–72 h. However, roughly 7 days after induction, protection can no longer be detected. The molecular basis for ischemic tolerance occurs in three stages. During the *induction stage*, molecular sensors (mostly receptors, channels, and regulators) are activated through transcription factors. In the *transduction stage*, certain protein kinases, transcription factors, and para- and autocrine mediators, such as growth factors, amplify the conditioning signal, thereby preparing the *effector stage*. In this stage, proteins with direct protective properties (antiapoptotic, anti-inflammatory, antioxidative, etc.) are activated. The transcription factor hypoxia-inducible factor-1 (HIF-1) is a key regulator of the cellular response to conditions of reduced oxygen availability. After hypoxic/ischemic stimulation, it is one of the main regulators of ischemic tolerance and also the target of a variety of clinically approved (and experimentally exploited) drugs. Among others, HIF-1 induces the expression of erythropoietin (EPO). EPO is released by astrocytes and binds to the neuronal erythropoietin receptor. Via activation of cascades downstream of

phosphoinositol-3 kinase, the proapoptotic protein BAD is phosphorylated, thereby inactivated. Apart from this paracrine cascade, a host of antiexcitotoxic, anti-inflammatory, and antiapoptotic mechanisms, including programs for regeneration and repair, have been implicated to mediate endogenous tolerance.

Clinically, transient ischemic attacks (TIAs) have been ascribed to present a preconditioning stimulus, and studies in patients that had a TIA before they suffered from a stroke indicate that ischemic tolerance also exists in humans. After a TIA, brain infarcts were smaller when compared to patients without preceding TIA. Furthermore, remote conditioning is used as a tool to induce ischemia tolerance in a variety of clinical settings. Several clinical trials are under way which explore the therapeutic feasibility of exploiting endogenous tolerance through the application of conditioning strategies or effector molecules such as EPO for stroke therapy.

Bench to Bedside: Clinical Implications of Ischemic Stroke

Ischemic stroke is a disease with high mortality and lifelong morbidity. Due to demographic changes in many countries, resulting in an overaged population, dramatic increases in stroke incidences in the Western world but also in developing countries can be anticipated. However, in some low- to middle-income countries, increasing rates of stroke incidence over the past years have resulted in incidence levels higher than in developed countries. Until now, therapeutic options for acute ischemic stroke are very limited and restricted to a narrow time window after the onset of symptoms. Restoration of blood flow, typically by recanalization of an occluded cerebral artery, critically depends on rapid recognition of typical stroke symptoms and fast initiation of treatment in a specialized stroke unit.

Cerebrovascular Anatomy and Major Cerebral Artery Territories

Typically, ischemic stroke is the result of an occlusion of one or more brain-supplying arteries. Depending on the arterial segment occluded and the size and functional relevance of the downstream brain parenchyma as well as collateral blood supply, different neurologic deficits can occur.

Four main arteries ensure blood supply to the brain: two internal carotid arteries (ICAs) and two vertebral arteries (VAs). The ICA ascends vertically in the neck, extending from the common carotid bifurcation to the base of the skull. It enters the base of the skull through the carotid canal. After giving off several branches such as the posterior communicating artery, it terminates at the bifurcation into the anterior and middle cerebral arteries. The two VAs arise from the subclavian arteries, enter the skull through the foramen magnum, and join to form the basilar artery (BA). The BA stretches from the pontomedullary junction to the pons-midbrain junction where it bifurcates into the right and left posterior cerebral arteries (PCAs). The carotid circulation, consisting of both intracranial ICAs, both anterior cerebral arteries (ACAs, A1 segments), and the anterior communicating artery, which connects left and right ACAs, and the vertebrobasilar circulation, consisting of the BA, both PCA and both posterior communicating arteries form the circle of Willis at the base of the

brain. The circle of Willis provides important collateral circulation to the brain in case of occlusion of the ICA or BA. The ACA supplies the medial surface of the cerebrum and the upper border of the frontal and parietal lobes. The MCA supplies the largest part of the brain hemisphere including the lateral surface of the cerebral hemisphere as well as the deep structures of the frontal and parietal lobes. The vertebrobasilar system including the PCA supplies the upper spinal cord, brain stem, labyrinth, cochlea, cerebellum, subthalamus, portion of thalamus, and the temporooccipital lobes.

Risk Factors of Ischemic Stroke

The most common risk factors of ischemic stroke include hypertension, atrial fibrillation, diabetes, smoking, hyperlipidemia, and asymptomatic and symptomatic carotid stenosis.

Clinical Syndromes of Ischemic Stroke

When admitting a patient with ischemic stroke symptoms to the stroke unit, assessment of the temporal course of the neurologic deficits as well as the severity and functional significance of the deficits is essential for the decision of the individual therapeutic strategies. Therefore, the following temporal patterns are often distinguished:

Transient Ischemic Attacks (TIAs)

TIAs are characterized by a temporary episode of a focal neurologic deficit. They are caused by a reversible restriction of the blood supply to a particular area of the brain. TIAs are characterized by a sudden and unprovoked onset, with a maximum intensity of symptoms at onset or very shortly after the onset of symptoms. By definition, symptoms last for a maximum of 24 h but can last significantly shorter. As TIAs may herald a full stroke, it is important to correctly diagnose such an episode to identify the arterial territory affected by exact assessment of the neurologic symptoms. The risk of a stroke in the first 3 months after a TIA is ~15%. However, most strokes occur in the first 2 days.

Symptoms of a TIA in the carotid artery circulation include, for example, contralateral weakness, contralateral numbness, dysphasia, dysarthria, amaurosis fugax, and/or contralateral homonymous hemianopia. In contrast, the following symptoms are indicative for a TIA in the vertebrobasilar circulation: bilateral or shifting weakness, ataxia, imbalance, bilateral or shifting numbness, dysarthria, diplopia, and/or partial or complete blindness in both homonymous visual fields.

The Anterior Cerebral Artery Syndrome

Occlusion of the ACA occurs in only 0.6–3% of cerebral infarctions. The clinical manifestations of ACA infarction depend on the site of occlusion and the status of collaterals. Clinical symptoms of a unilateral ACA infarction include a contralateral sensomotor paresis involving primarily the lower extremity and, to a lower extent, the upper extremity, in particular the shoulder. Furthermore, symptoms like lack of initiative (abulia) and paratonia are often present. Patients with bilateral ACA

occlusion may present with akinetic mutism, paraplegia, incontinence, and amnesia with apathy.

The Middle Cerebral Artery Syndrome

The MCA is the largest branch of the ICA. The MCA territory is the most commonly affected in ischemic stroke. Clinical symptoms include contralateral weakness affecting the face, the arm, and, to a lesser extent, the leg. Furthermore, perioral and distal upper limb sensory dysfunction may occur. Patients with MCA territory infarction may also present with a transient tonic deviation of the eyes and head toward the side of the lesion. Infarctions in the dominant hemisphere for language are clinically characterized by nonfluent, fluent, conduction, or global aphasia, depending on the site and extent of the stroke. Infarction in the nondominant hemisphere causes inattention, neglect, denial, apractic syndromes, and impaired prosody. Furthermore, MCA infarction may give rise to contralateral homonymous hemianopia. Complete ("malignant") MCA territory infarctions have a poor outcome. These patients present with severe hemiparesis, forced eye and head deviation global aphasia (dominant hemisphere), or severe hemineglect (nondominant hemisphere). With a latency of several hours to a few days, patients show a progressive diminishing level of consciousness, which is secondary to space-occupying ischemic brain edema. Subsequently, brain shifts and herniation occur.

The Posterior Cerebral Artery Syndrome

Infarction in the PCA territory results in contralateral homonymous hemianopia. Furthermore, more complex visual changes, such as formed and unformed visual hallucinations, visual or color agnosias, or prosopagnosia, may occur. Also, some alterations of sensation may be present, including paresthesia, or altered position, pain, and temperature sensations. Right hemispheric PCA infarctions often cause contralateral visual field neglect. Proximal PCA occlusion may simulate MCA occlusion when it causes hemiparesis, hemianopia, hemispatial neglect, aphasia, and sensory loss or inattention.

Lacunar Stroke

Ischemic stroke due to arterial hypertension usually affects small vessels or penetrating arteries and causes lacunar ischemic strokes. Lacunar infarcts are located in the deep regions of the brain or brain stem and usually have a range in diameter from 0.5 to 15 mm. The most frequent sites of lacunar infarcts are the putamen, basis pontis, thalamus, posterior limb of the internal capsule, and the caudate nucleus. Lacunar ischemic infarcts represent up to 20% of all strokes and therefore are an important subgroup of ischemic stroke.

Syndromes of lacunar stroke include:

- Pure motor hemiparesis

  This clinical syndrome includes a unilateral hemiparesis or hemiplegia, involving the face, the arm, and, less pronounced, the leg. Furthermore, mild dysarthria may occur. The lacunar infarct is often located in the internal capsule,

corona radiata, or basis pontis. In contrast, no aphasia, apraxia, or agnosia and no sensory, visual, or higher cortical disturbances should be present.

- Pure sensory stroke

  This lacunar syndrome is characterized by numbness, paresthesias, and a unilateral hemisensory deficit. Corresponding lacunes often involve the ventroposterolateral nucleus of the thalamus. Additionally, ischemic lesions can be found in the internal capsule/corona radiata, subthalamus, midbrain, parietal cortex, medial lemniscus, or in the paramedian dorsal pons.
- Ataxic hemiparesis

  Ataxic hemiparesis is characterized by mild to moderate hemiparesis, predominantly in the leg, and ipsilateral cerebellar ataxia of the arm and leg. Lacunar infarcts, which correspond to these clinical symptoms, can be found in the contralateral posterior limb of the internal capsule, the contralateral basis pontis, contralateral thalamus capsule, contralateral red nucleus, corona radiata, lentiform nucleus, or in the superior cerebellar artery territory.
- Dysarthria-clumsy hand syndrome

  This syndrome is often caused by a lacune in the depth of the basis pontis between its upper third and lower two-thirds. It is characterized by supranuclear facial paresis, deviation of the tongue, dysarthria, dysphagia, loss of fine motor control of the hand, and an extensor plantar response.

Diagnostic Strategies in Acute Ischemic Stroke

When a patient has been admitted to the emergency room with acute symptoms of stroke, the most critical question is whether the patient has suffered from an ischemic or a hemorrhagic stroke. Important hints for this distinction can already be acquired by taking a complete past and present medical history of the patient and by the clinical examination. However, even for the most experienced clinician, it is impossible to clearly distinguish between ischemic and hemorrhagic stroke. Therefore, cerebral imaging is crucial in this acute situation. In most cases, cranial computed tomography (CCT) is performed. Although definite signs of acute ischemic stroke often cannot be identified by CCT within the first few hours of stroke, it allows ruling out intracranial hemorrhage. Therefore, CCT is sufficient as an acute diagnostic measure. Experienced neurologists and neuroradiologists are also often able to identify early signs of ischemic stroke, for example, in the MCA territory. These early signs include the "hyperdense media sign," a hyperdense dot in the course of the MCA which represents the site of the thrombus, and/or a beginning hypodensity in the nucleus lentiformis, the insula, or the cortex. An additional angio-computed tomography (CT) using contrast agent allows to clearly identify the arterial occlusion. Furthermore, in many specialized stroke centers, perfusion CT is available. This imaging tool allows the identification of hypoperfused brain areas and thereby the presumed size of infarction. By the use of this multimodal CT imaging sequence in patients with acute ischemic stroke, it is possible to gather sufficient information on the location and predicted size of ischemic stroke as well as on further brain regions which might be at risk for infarction. Therefore, based on this information by CT, a decision on further therapeutic steps can be made in many cases.

Sometimes, in particular, in patients with brain stem or cerebellar infarctions or in cases of small ischemic stroke (i.e., lacunar infarctions), CT is insufficient to identify the ischemic stroke. In these cases, magnetic resonance imaging (MRI) should be performed. By MRI, ischemic stroke can be clearly identified already in the early stages. Because of that, MRI is superior to CCT in acute ischemic stroke diagnostics. MRI in acute ischemic stroke patients includes several sequences. T2* sequence allows excluding acute hemorrhagic stroke. Diffusion-weighted imaging (DWI) is an MRI sequence that highly sensitively identifies even small ischemic strokes by detecting impaired molecular movements within the affected brain parenchyma due to the ischemic cytotoxic edema. By magnetic resonance angiography, stenoses, occlusions, or aneurysms of cerebral arteries can be identified. In patients with a suspected arterial dissection, a T2-weighted fat-suppression sequence can identify the intramural hematoma. Fluid-attenuated inversion recovery (FLAIR) sequence is valuable in the diagnosis of subacute and chronic ischemic strokes as well as lacunar infarctions and other pathologic brain lesions. Furthermore, perfusion-weighted imaging (PWI) sequence should be performed. The main advantage of MRI over CCT in the diagnostic procedures for acute ischemic stroke is that even small ischemic areas also in the brain stem and cerebellar regions can be clearly identified by MRI in the initial stages after the onset of symptoms. Furthermore, tissue at risk for infarction can be identified by analysis of the PWI-DWI mismatch. A mismatch as an indicator of tissue at risk is present in cases of a large lesion by PWI (area of reduced cerebral perfusion) and small DWI lesion (area of cerebral infarction).

Another diagnostic tool, which can provide valuable information on the status of large extracranial and intracranial arteries, is Doppler and duplex sonography. It is an inexpensive examination that can be easily applied bedside. Its main application area is certainly follow-up assessment of extracranial and intracranial vascular stenoses and occlusions as well as evaluation of the blood supply by collateral circulation in the individual patient. Furthermore, transcranial Doppler (TCD) allows detection of microemboli-derived ultrasound signals which can originate from high-grade ICA stenosis. Also, the use of so-called microbubbles or ultrasound contrast agents with TCD is an established method to detect a right-left shunt in the heart through a patent foramen ovale which can be a potential source of cerebral embolism (paradoxical embolism). Additionally, a functional cerebrovascular reserve of several intracranial vascular territories can be assessed by TCD using a hyperventilation test or acetazolamide. Evaluation of the cerebrovascular territory is important for the assessment of treatment relevance of high-grade arterial stenoses of extra- or intracranial brain-supplying arteries. Digital subtraction angiography (DSA) is the gold-standard diagnostic tool for the evaluation of pathologies in extra- and intracranial circulations. Furthermore, DSA is used for immediate interventional therapy of cerebrovascular pathologies, for example, recanalization of vessel occlusions by intra-arterial thrombolysis. Even though systemic thrombolysis is more commonly used to date, intra-arterial thrombolysis is still the treatment option of choice in patients with acute basilar occlusions.

Cardioembolic ischemic stroke is a common etiologic entity. In order to clarify the potential cardiac source of cerebral embolism, several diagnostics are recommended. Distribution pattern of multiple acute embolic ischemic strokes in

different vascular territories analyzed by cerebral imaging (CCT or MRI) can be suggestive for cardiac embolism. Electrocardiography (ECG) and Holter ECG are recommended for all patients with acute ischemic strokes in order to rule out evident or intermittent atrial fibrillation. Transthoracic echocardiography and transesophageal echocardiography are diagnostic measures of choice in the verification of cardiac embolism, for example, patent foramen ovale, detection of thrombi in the left atrial auricle, and endocarditic vegetations.

Treatment of Patients with Acute Ischemic Stroke

According to current guidelines, it is recommended that patients with suspected acute ischemic stroke should be treated on a ward specialized in the acute treatment of ischemic stroke. Treatment of patients with acute ischemic stroke on such a "Stroke Unit" can be divided into specific (i.e., recanalizing) therapies and general supportive care.

Recanalizing Therapy

To date, the only approved specific therapeutic option for patients with ischemic stroke in the acute setting is recanalizing therapy using either thrombolysis with recombinant tissue plasminogen activator (rtPA) or thrombectomy. Thrombolysis was initially approved for a 3-h time window after the onset of stroke based on the results of the NINDS trial in 1995. According to this trial, patients treated with rtPA within 3 h after the onset of ischemic stroke symptoms were at least 30% more likely to have minimal or no disability at 3 months. In 2009, the time window for rtPA thrombolysis was extended after the publication of the ECASS-3 trial. rtPA given intravenously at a total dose of 0.9 mg/kg body weight is now approved within a 4.5 h time window. Numerous attempts have been done to further extend the time window of thrombolysis with rtPA or other experimental thrombolytics. Furthermore, there are increasing data on the efficacy of revascularization using mechanical intra-arterial devices. However, none of these therapeutic efforts have been approved, yet. Therefore, these experimental therapeutic options remain reserve strategies on an individual basis. The classic exception in which thrombolysis with rtPA should be considered even beyond the 4.5 h time window is a BA thrombosis. Patients with BA thrombus and without successful recanalization of BA have a mortality of $>$90%. Because of that, thrombolytic or other mechanical recanalizing treatment strategies should be attempted in these patients at a low threshold.

Thrombectomy, i.e., mechanical retrieval of a blood clot of a large cerebral artery, is now an approved therapy in many countries. Several clinical trials have proven the efficacy of this treatment and whenever possible (i.e., there are no contraindications), it should be combined with thrombolysis. The general time window for thrombectomy is 6 h; however, this can be extended to up to 24 h depending on the circumstances (see guidelines for details).

General Supportive Care

- Arterial blood pressure

  According to current guidelines, elevated arterial blood pressures are tolerable in the acute phase of ischemic stroke, even though chronic arterial hypertension is

the main risk factor for ischemic strokes. The rationale for keeping the blood pressure elevated within the first few days after ischemic stroke is the consideration that increased blood pressure guarantees sufficient perfusion pressure in the penumbra and, thereby, helps to prevent the propagation of the ischemic injury. However, excessive hypertensive episodes (i.e., systolic blood pressure >210 mmHg) should be avoided due to the increased risk of secondary hemorrhage into the ischemic tissue. After rtPA thrombolysis, arterial blood pressure should not exceed 185/110 mmHg. Conversely, an excessive drop in blood pressure should also be avoided. In the chronic phase after ischemic stroke, arterial blood pressure should be carefully adjusted within the normal range.

- Blood glucose level

  Increased blood glucose levels are common after ischemic stroke, and they are associated with poor clinical outcomes. Conversely, normalization of elevated blood sugar is related to a higher probability of survival. Therefore, current ischemic stroke guidelines recommend strict normalization of blood sugar in the acute phase after ischemic stroke. At this, the treatment of choice is administration of insulin. On the other hand, hypoglycemia should be avoided implicitly.

- Body temperature

  Fever is common in acute ischemic stroke patients. Fever within 24 h after ischemic stroke is associated with a doubling of the mortality rate. Furthermore, experimental ischemic stroke studies have demonstrated that hyperthermia is associated with increased infarct volumes and poorer functional outcomes. An increased body temperature should prompt a search for infection and appropriate antibiotic treatment. Even though studies concerning antipyretic medication have been inconclusive, treatment of raised body temperature (>37.5 °C) with acetaminophen, metamizole, and/or physical cooling is well established in the treatment of acute ischemic stroke patients.

Outlook

Intensive experimental and clinical research has greatly improved our pathophysiological understanding of cerebral ischemia. However, to date, the sole safe and effective therapy is the restoration of blood flow to the affected brain territory. Complex cascades involving excitotoxicity, oxidative and nitrosative stress, periinfarct depolarization, inflammation, apoptosis-like mechanisms, and many more have been described in different models of cerebral ischemia. However, despite impressive results in animal experiments, so far translation of many preclinical results into human stroke therapy has largely been unsuccessful. Reasons for this dilemma include weaknesses in the design of animal studies as well as (pre-)clinical trials. At the same time, many pathophysiological mechanisms remain unsolved. Recent experimental data demonstrates that stratification of molecular mechanisms into “beneficial” or “detrimental” mechanisms is an improper simplification. Further research is required to identify more suitable molecular targets. Since multiple

pathways cause cell death in stroke, it seems reasonable to develop combination therapies targeting several of these mechanisms simultaneously. Despite the complex pathophysiological mechanisms, there is the reason for optimism, as advances in molecular and cell biology, neuroimaging, as well as clinical practice provide tools for better translation of discoveries from bench to bedside.

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