Neuroprotection

Models, Mechanisms and Therapies

Edited by
Mathias Bähr

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Preface

In the last decades, the scientific community as well as the public has been overwhelmed with a tremendous amount of data on the cellular, molecular and physiological mechanisms of neuronal proliferation, differentiation, maintenance and degeneration. A plethora of animal models of various neurological disorders has been introduced and used to delineate the mechanisms of cell death and highlight potential targets for neuroprotective or neurorestorative intervention strategies. With great enthusiasm, the complete deciphering of the human genome and the genetic information of various other species has been announced and raised the hope of a final victory over many fatal human diseases. Findings about the genetic or molecular causes of human disorders that were reproduced in animals and positive results from experimental therapies were generalized for human patients, and new experimental treatments were quickly transferred to clinics, sometimes speeded up by high expectations of the public as well as managers from pharmaceutical companies.

However, by the same token, many clinical studies which were introduced on the basis of positive data with new pharmacological substances or effective procedures in animal models did not show positive results in humans, and several trials had to be stopped, due to adverse effects which led to a significant deterioration in some patients.

From a multitude of substances tested in basic research models, only few have reached clinical testing in patients thus far. Among those substances are neurotrophic factors, mitochondria-stabilizing agents, anti-oxidants, anti-toxins, antibiotics, glutamate receptor and calcium channel blockers as well as caspase-inhibitors (Kermer and Bähr, 2002). However, none of them has so far led to a substantial breakthrough in neurological or psychiatric therapy. Thus, one has to ask why so many promising drugs with positive effects in basic research models failed in the clinic. This is not easy to understand, and there is certainly not a single answer. However, some general aspects can be mentioned which are discussed in more detail in the various chapters of this book:

First of all, in animal models, the modes of application, the delay between onset of a pathology and therapy and many side effects are completely different to the human situation. Thus, a substance may show a profound effect after intraparenchymal or intraventricular application minutes after onset of ischemia in animals, but the systemic application hours after onset of a stroke in humans does

not result in a timely and quantitatively sufficient concentration in the affected region or cell in the CNS.

Secondly, as mentioned earlier, in standardized animal models, mostly young and otherwise healthy rodents are used. In contrast, patients with neurological disorders, e. g. stroke, are often old with a substantial co-morbidity, which may result in many cross-reactions of a new drug with existing medications and adverse effects that can not be anticipated in young and healthy animals. Finally, the time of onset, the course and the outcome of a given insult vary substantially in patients and, depending on the selection criteria for clinical studies, a potentially effective drug may be given to patients where there is nothing left to rescue at all, or the criteria which are used in animals to demonstrate efficacy are not available for patients (e. g. histological measure of cell survival rates or tissue preservations in animal models which can not be applied in human patients).

As a consequence, the whole concept of developing or introducing new drugs on the basis of animal (model) data was challenged, and many big pharmaceutical companies stopped or significantly reduced their efforts to develop new "neuroprotective" substances in their basic research departments.

Thus, it appears to be timely to present a comprehensive review on our current knowledge in the field to analyse the potential as well as the limitations of the available model systems for many highly relevant neurological disorders such as stroke, trauma, neurodegenerative disorders or inflammatory diseases of the CNS. Furthermore, it seems to be necessary to have a closer look at some general problems that evolve when data from animals, mostly young and healthy rodents, are to be translated into clinical settings in order to learn from the errors for our future planning of neuroprotective or neurorestorative therapies.

Finally, new results from basic as well as applied research need to be presented and evaluated which may open completely new avenues for future therapy concepts. To that end, internationally recognized outstanding experts in their respective fields from several countries have contributed to this first edition of Neuroprotection – Models – Mechanisms – Therapies.

We hope that this book provides a guideline for non-experts for a better understanding of the complexity of data that are generated in basic research experiments and the pitfalls of translational research on the one hand and a detailed overview and basis for discussions and future developments in the field for academics involved in basic research or applied neurosciences on the other.

Göttingen, January 2004 *Mathias Bähr*

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I
Neurological Disorders – Epidemiology, Clinical Overview, and Model Systems

1
Stroke

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Abstract

The current understanding of stroke pathophysiology is basically founded on experimental models. Among these, *in vitro* models with primary cultures of cerebral cells permit stroke pathophysiology to be examined on a molecular level, while animal models (mainly mouse and rat) are used to evaluate medical intervention. There is a highly complex sequence of events leading to the eventual ischemic cerebral damage that follows a well-defined spatio-temporal pattern. Overwhelming excitotoxicity leads to early necrotic cell death in what is to become the core of the infarction, while the tissue damage in the surrounding zone called penumbra happens on a longer time scale. The excitotoxic or inflammatory mechanisms are milder, bearing the biochemical hallmarks of apoptosis. The brain cells, challenged by such a large-scale assault, activate endogenous protective programs. These have been studied by experimentally inducing ischemic tolerance (i. e. ischemic preconditioning). Importantly, cerebral ischemia not only affects the brain, but also impacts other systems. For example, stroke induces dramatic immunodepression through over-activation of the sympathetic nervous system. As a result, severe bacterial infections such as pneumonia occur. The complex signaling cascades not only decide over cell survival in the brain and the neurological deficit, but also over mortality after stroke from extracerebral complications. Their ability to govern not only the maturation of the eventual infarction but also the immune system make them a promising target for intervention and the development of neuroprotective drugs.

1.1
Introduction

In the US more than 600,000 people per year suffer from strokes, and among acutely hospitalized neurological patients stroke patients make up the largest share – about 50 %. Currently, there are about 4 million stroke survivors [1] in

the US. Mortality from stroke is an estimated 25 %, which makes it the third major cause of death in industrialized countries. Due to the high rate of severe permanent disability, stroke is a burden not only for the affected patients and their families, but also for national economies: In the US, it is estimated that the annual costs caused by strokes ranges between 30 and 40 billon dollars [2, 3]. In the UK, the cost of one individual patient amounts to £ 30,000 over 5 years [4].

The term stroke accommodates a variety of different conditions. About 85 % of all strokes are caused by cerebral ischemia due to vessel occlusion. Primary cerebral bleeding is rare in comparison –15 %. Of the ischemic strokes, 75 % are caused by emboli, of either arterial or cardial origin, while microvascular occlusion, i. e. hyalinosis or *in-situ* thrombosis is responsible for 20 % of cases. Hemodynamic ischemia, caused by stenoses of brain-supplying arteries, account for less than 5 % of ischemic strokes [5, 6].

The prospective risk of suffering an ischemic stroke is partially a function of social and behavioral (nutrition, tobacco use, stress) factors and longstanding disorders like hypertension, diabetes, disorders of cholesterol and lipid metabolism, and obesity. Atherosclerosis is not only the main underlying condition in ischemic stroke, but also in coronary heart disease and peripheral vascular disease. Moreover, the genetic background of affected individuals is coming under increasing scientific scrutiny, as might be expected for familial stroke conditions like CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leucencephalopathy), which is characterized by relapsing subcortical ischemia. The condition is caused by a mutation in the *notch3*-gene on chromosome 19 [7, 8]. MELAS (mitochondrial encephalopathy, lactate acidosis, stroke-like episodes) is another rare familial stroke disorder, characterized by migraine, grand-mal seizures, and recurrent cortical infarctions. The condition is caused by a range of mutations in the mitochondrial genome, which explains its maternal inheritance. The severity of the phenotype depends mainly on the mutation locus and on the proportion of mutated mitochondrial genomes in the cerebral mosaic (for review see [9]). However, family and twin studies suggest that genetic factors are likely to be involved in common types of ischemic stroke, not just in rare and well defined familial stroke disorders [10–13].

A locus on chromosome 5q12 described for the Icelandic population seemed to increase stroke susceptibility significantly [14]. The responsible gene has been identified as phosphodiesterase 4D (PDE4D). The risk-conveying polymorphisms are located in the gene-regulatory part. This hints at a defect in the regulation of the encoded cAMP degrading protein [15]. Phosphodiesterase 4D belongs to a group of proteins that are drug targets in the treatment of asthma, erectile dysfunction and inflammation.

Symptoms of focal cerebral ischemia depend on the individual affected vessel with its typical supply territory. Table 1 summarizes the frequency of affection [16] and the typical clinical syndromes for the main brain arteries. Stroke mortality is rated between 20 and 30 %. Unfavorable prognostic factors are old age, initial coma, papillary asymmetry, coronary heart disease and heart failure. Pyrexia and infections (pneumonia in particular) deteriorate the prognosis particularly during

the initial phase (see below). Of the surviving patients, one third improves within a week, 40 % remain unchanged in their disability, and 20 % deteriorate further during the first week [17].

Table 1.1 Territorial stroke syndromes.

Anterior territory		
MCA	(≈60 %)	hemiparesis mainly arm, hemihypaesthesia, hemianopia, dysphasia or neglect
ACA	(4 %)	hemiparesis mainly leg, urinary incontinence, apraxia
AchA	(8 %)	hemiparesis, hemihypaesthesia, hemianopia
Posterior territory		
VA/BA	(10 %)	vertigo, diplopia, bilateral hypaesthesia and paresis, crossed syndromes, amaurosis, ataxia, headache, coma
Cerebellum (PICA/ AICA)	(7 %)	headache, ataxia, vertigo, gaze palsy, facial weakness, deafness
PCA	(9 %)	hemianopia, dyslexia, visual agnosia

A great deal of our knowledge about the pathophysiology of stroke comes from experimental research. The experimental animal models follow two main paradigms: One is the model of focal cerebral ischemia as a model of ischemic stroke. The other is the model of global cerebral ischemia as model of circulatory arrest. For obvious reasons, we will focus mainly at studies of focal cerebral ischemia. The bulk of experimental studies has been carried out with rats and mice, although some primates have been used. In rodents, ischemia is mostly induced by intravascular occlusion of the MCA, using a monofilament just exceeding the critical vessel diameter. Depending on the duration of occlusion, we distinguish permanent from transient ischemia models. The latter are also used as models for spontaneous reperfusion or for the state after successful lysis therapy with recombinant tissue plasminogen activator (rtPA) in humans, respectively.

In models of cerebral ischemia perfusion to the brain is impeded by some form of manipulation. Since the essence of ischemic stroke is vascular occlusion, it is not surprising that in these models the extent of the eventual infarction can be predicted quite accurately from the degree of reduction in regional cerebral blood (rCBF) flow. Thus, if the rCBF is reduced to less than 25 % of normal the likelihood of infarction in a given volume of brain tissue greater than 95 %. In contrast, the likelihood of infarction is less than 5 % if rCBF does not fall below 50 % of normal. These thresholds have been established in comparative human PET and MRI studies [18] and correspond with experimental data from animal models [19]. Thus, the initial reduced rCBF determines the extent of the anticipated infarction. This, however, holds only with the provision that a spontaneous or therapeutic reperfusion does not take place.

We now look at ischemic infarction as the result of a complex and prolonged process of infarct maturation rather than a simple result of reduced regional perfu-

sion. As brain tissue has a high demand for oxygen and glucose, a disruption of perfusion leads to substrate depletion within few minutes, while toxic metabolites accumulate. The ensuing cellular energy deficit leads to a collapse of the established ion gradients and the membrane potential. Neurons and glial cells depolarize. Depending on the extent and the duration of this energy deficiency, the cells will suffer not only a functional but also a structural breakdown. The highly complex sequence of events within the ischemic area follows a fairly well defined stereotypic spatio-temporal pattern, which we will discuss below in more detail. The concept of the ischemic **penumbra** is crucial to the understanding of these mechanisms. The cascade of ischemic damage begins with **excitotoxicity**, the formation of reactive **oxygen free radicals**, the increasing **tissue acidosis** and the occurrence of **periinfarct-depolarizations**. It is followed by the stages of **inflammation** and programmed cell death (**apoptosis**). This is associated with **DNA damage** that, in turn, induces **DNA repair programs**. Although the process is not yet fully understood, we know that chromatin re-modeling, i. e. **epigenetic mechanisms**, and the activation of transcription factors induce complex **gene programs**. These changes initiate the expression of destructive proteins involved in inflammation and apoptosis, as well as a host of protective genes that help repair the ischemic damage. It is the activation of these protective genes that builds up **ischemic tolerance**. Among the many newly discovered protective mechanisms, **endogenous** and **exogenous cell replacement** have met with a lot of interest. Apart from these autochthonous mechanisms of the brain tissue, there are other mechanisms on a systemic scale, which bear important clinical significance. For instance, the phenomenon of **stroke-induced immunodepression** can help to understand why stroke patients are at such high risk of contracting serious bacterial infections. Neuroprotective treatment must be based on an understanding of these mechanisms.

1.2 The Penumbra Concept

In the ischemic brain, we commonly distinguish two tissue volumes – the core of the infarction and the surrounding zone, known as ischemic penumbra [20] – the underperfused and metabolically compromised margin surrounding the irrevocably damaged core. Core and penumbra are characterized by two different kinds of cell death: necrosis and apoptosis (which is also called programmed cell death or delayed neuronal cell death). The severe perfusion deficit in the core causes a breakdown of metabolic processes, cellular energy supply and ion homeostasis, which causes the cells to lose their integrity within minutes. Thus, acute necrosis of cell and tissue prevails in the core. In the penumbra, some residual perfusion is maintained by collateral vessels, which may be unable to maintain the full functional metabolism, but prevents immediate structural disintegration. However, over time, the alteration of cellular homeostasis causes more and more cells to die, and the volume of the infarction increases. The penumbra has thus to be considered as tissue at risk during the maturation of the infarct. In this region,

apoptosis and inflammatory signaling cascades play an important role. It may initially constitute 50 % of the volume that will end up as infarction. The mechanisms that lead to delayed cell death within the penumbra are the subject of intense research, as they provide targets for a specific neuroprotective therapy in brain regions challenged by ischemia, but which are still viable (for a review see [19, 21]).

1.3 Excitotoxicity

The depolarization of neurons and glia due to local energy deficit causes the activation of voltage-gated calcium channels and the release of excitatory amino acids into the extracellular space. Glutamate in particular, which, under normal cellular energy conditions, would be immediately taken up pre-synaptically or through astrocytes, now remains in the extracellular space where it accumulates dramatically. Through the activation of glutamate receptors NMDA and AMPA, the intracellular Ca^{2+} level rises. Furthermore, metabotropic glutamate receptors are activated through the induction of phospholipase C (PLC) and inositol triphosphate (IP_3), and calcium is mobilized from intracellular stores.

Furthermore, the over-activation of AMPA receptors causes a rise of sodium and chloride concentrations. Altogether, the result is a massive disturbance of ion homeostasis, accompanied by passive water influx and cell edema. Ultimately, these massive changes in cell volume account for osmotic cell lysis. This lytic type of cell death, also referred to as necrosis, is primarily observed in the core of the infarction. Cells that escape this most dramatic form of disintegration, as they can not found in the core but in the penumbra where excitotoxicity may be an initiator of molecular events that lead to apoptosis and inflammation (for an overview see [21, 22]).

1.4 Oxygen Free Radicals

As a consequence of ischemia and particularly of reperfusion, reactive oxygen free radicals such as superoxide, hydrogen peroxide and hydroxyl radicals are generated. Nitric oxide is generated via the activation of the calcium-calmodulin-dependent nitric oxide synthase (NOS); it reacts with superoxide radicals and forms thus the highly reactive peroxy-nitrite radical. Further sources of oxygen free radicals in the damaged brain tissue are the breakdown products of the adenosine phosphates, which contribute to radical production via xanthine oxidase and the iron-catalyzed Haber-Weiss reaction. The many different radical species that are thus formed can react with virtually any cellular components (carbohydrates, amino acids, DNA, phospholipids) and damage them. The peroxidation of membrane lipids releases further radicals – and further glutamate. Oxygen free radicals gain even more

significance when new oxygen reaches the damaged tissue by virtue of reperfusion, or in the penumbra where oxygen supply has not ceased entirely (overview in [21, 22]).

Hypoxia itself as well as the elevated intracellular concentration of calcium ions and free radicals disrupt the function of neuronal mitochondria. Consequently, a so-called mitochondrial permeability transition pore (MPT) in the mitochondrial membrane may form. Besides impeding ATP production through loss of mitochondrial potential, the MPT leads to mitochondrial swelling, a burst of free oxygen radicals, and the release of pro-apoptotic molecules. Thus a vicious cycle of further disintegration is fuelled (see below, for review [21, 23]). This vicious cycle is counterbalanced in part by anti-oxidative enzymes like the manganese-superoxide dismutase (Mn-SOD) and the cytosolic forms of the copper-zinc superoxide dismutase (CuZn-SOD). These may prevent the breakdown of the mitochondrial membrane and, thus, the release of cytochrome C, which would be the trigger of apoptosis (see below and for review [24]).

1.5 Tissue Acidosis

In the context of stroke pathophysiology, the proton balance is intimately linked with the glucose metabolism. With reduced oxygen availability, anaerobic glycolysis as only remaining source of ATP production leads to tissue acidosis. It has long been assumed that this acidosis was one of the main noxious mechanisms in ischemic stroke. This so-called 'lactate-acidosis-hypothesis' is often quoted as explanation for the "glucose paradox" of cerebral ischemia. This paradox refers to the observation that excessive supply of glucose, the most important source of energy of the brain, during focal cerebral ischemia does not reduce tissue damage as one should think but, instead, augments it [25]. However, by which mechanism this happens and, in fact, whether levels of acidosis reached in brain ischemia can generate brain tissue damage at all is still far from being clear. Possibly, the pH dependent transition of Fe(III) to Fe(II) and the release of iron from molecular storages lead to a facilitation of the Haber-Weiss reaction that forms toxic free oxygen radical species (see above). Besides the production of different species of oxygen free radicals, acidosis also interferes with intracellular protein synthesis. However, the lactate-acidosis-hypothesis is not unchallenged. Particularly the fact that acidosis blocks the NMDA-receptor and thus has an anti-excitotoxic effect indicates the complexity of the role that acidosis plays in cerebral ischemia (for a review [21]).

A similarly hotly debated topic are the findings on hyperglycemia during stroke. Experimental data from animal models show a detrimental effect of hyperglycemia during focal cerebral ischemia [26–28]. Clinical data also suggest that hyperglycemia during the acute phase of stroke worsens prognosis [29–31]. Persisting hyperglycemia beyond the acute phase is also an independent prognostic factor for larger infarct volume and poorer functional outcome in stroke patients [32]. It is a matter of debate whether these observations are due to a causal relationship or if hypergly-