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New cerebral protection strategies

[Neuroanaesthesia]

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Abstract

Purpose of review: This article presents an overview of the most recent and important strategies to reduce secondary brain damage.

Recent finding: There is currently no magic bullet available to protect the brain after neuronal injury. This is related to the complex pathophysiology of cerebral ischemia, which makes it unlikely that a single pharmacological intervention results in sustained neuroprotection. Analyses of clinical studies reveal that acute physiologic derangements (e.g. fever, hypertension and hypotension, hypoxemia, hypercapnia, hyperglycemia) are the most important predictors of unfavorable outcome after brain injury and have to be treated. The effectiveness of anesthetic agents to extend the ischemic tolerance of neurons has been demonstrated in experimental settings, but such benefits have not been demonstrated in humans. The effectiveness of osmodiuretics to decrease elevated intracranial pressure, a factor with relevance to outcome, has been demonstrated. Infusion of magnesium in patients with subarachnoidal hemorrhage can reduce the occurrence of delayed ischemia caused by cerebrovascular spasm. The prophylactic administration of glucocorticoids should be avoided. While the positive effects of chronic administration of statins to reduce the incidence of stroke has been demonstrated in several clinical studies, the protective effect of acute administration of statins after a cerebral insult has do be defined.

Summary: Control of physiological variables, avoidance of hyperthermia, intensive control of plasma glucose concentrations, use of anesthetic agents and osmodiuretics to control intracranial hypertension and the possible prophylactic administration of magnesium in patients at risk of vasospasm and of statins in patients with cerebrovascular risk factors are currently the most important strategies to reduce neuronal injury.

Abbreviations CBF: cerebral blood flow; ICP: intracranial pressure.

Introduction

Cerebral ischemia or hypoxia may occur as a consequence of shock, vascular stenosis or occlusion, vasospasm, neurotrauma, and cardiac arrest. The ischemic/hypoxic insult evokes a cascade of pathophysiological processes that result in two mechanisms of neuronal death: necrosis and apoptosis. Necrotic cell death occurs after a severe insult and is initialized by high lactic acid concentrations due to anaerobic glycolysis, depleted ATP-stores, increased membrane permeability, excessive release of excitatory neurotransmitters and edema formation leading to self-destructive intracellular processes. Apoptosis is an active form of cell death without edema formation, which requires production of regulating proteins and involves the activation of

caspases (ICE-like proteins) leading to progressive structural changes of biological membranes and the nucleosomal DNA (e.g. DNA fragmentation, chromatin condensation, and production of small particles consisting of cell debris (apoptotic bodies) over a period of days and weeks.

Strategies to protect the brain from ischemic/hypoxic insults are based on the understanding of these pathophysiological processes. Maintenance of normal cerebral perfusion pressure [1,2••], normoxia, and surgical decompression are by far the most important and effective neuroprotective interventions. Besides these treatment modalities, concepts of pharmacological brain protection include interventions to increase cerebral blood flow (CBF) in the ischemic territory, reduction of cerebral metabolism and intracranial pressure (ICP), inhibition of lactic acid accumulation and excitatory neurotransmitter activity, prevention of calcium-influx, inhibition of lipid peroxidation, and free radical scavenging.

Hypothermia

There is still major interest in thermal interventions applying moderate (29–32°C) or mild hypothermia (33–36°C). This is due to observations in laboratory animals and human trials using a small sample size, which show neuronal protection even with minimal reductions in brain temperature during periods of increased ICP or cerebral ischemia. Hypothermic protection is related to suppression of major biochemical processes such as decreases in cerebral metabolism and of excitatory neurotransmitter release and inhibition of accumulation of lipid peroxidation products and free radical generation. Other studies indicate that small changes in temperature balance CBF and metabolism and prevent postischemic hyperperfusion and hypoperfusion and brain edema formation.

Phase I and II small studies in patients following head injury, cardiac arrest, and stroke suggested that neurologic deficit and mortality was reduced when mild to moderate hypothemia is induced within 6–24 h following the insult and maintained for 24–48 h. So far, only larger trials in cardiac arrest have confirmed these findings. A meta-analysis of three randomized trials confirmed short-term neuroprotective effects and reduction of mortality by therapeutic hypothermia following cardiac arrest [3••], while long-term efficacy needs further evaluation.

In 46 patients with head injury moderate hypothermia improved neurological outcome after 3 months. These results were not confirmed by a prospective, controlled, randomized phase-III-investigation (National Acute Brain Injury Study: Hypothermia; NABISH) [4], however, possibly because of major intercenter variability in other aspects of patient management. In a subgroup analysis better outcome was associated with hypothermia in patients who were already hypothermic (<=35°C) on admission [5]. Therefore, a further study was initiated investigating the beneficial effect of hypothermia in these patients (NABISH-II trial).

After promising results in a pilot trial using intraoperative hypothermia (target temperature 33°C) during aneurysm surgery, the effect of hypothermia on neurologic outcome has been investigated in a multicenter trial (Intraoperative Hypothermia for Aneurysm Surgery Trial; IHAST) [6••]. The use of intraoperative mild hypothermia, however, had no beneficial effects on neurologic outcome after craniectomy in good-grade patients with aneurysmal subarachnoid hemorrhage.

While the protective effects of hypothermia are still undetermined, the unfavorable effects of hyperthermia are well known and have to be treated aggressively in patients with cerebral ischemia [7•].

Plasma glucose concentration

A detrimental link between hyperglycemia and deteriorated neurological outcome and larger infarct volume after experimental ischemic stroke, head trauma and subarachnoid hemorrhage has been demonstrated in animals and humans. An optimal level of plasma glucose concentrations in rats after focal cerebral ischemia is 108–126 mg/dl, because this was associated with the smallest infarct volume [8•]. If plasma glucose is further decreased by insulin administration, the low plasma glucose level (18–36 mg/dl) increased mortality compared with untreated rodents. Therefore, both hyperglycemia and hypoglycemia worsen outcome after neuronal damage in experimental settings. In addition to an effect on blood glucose, insulin itself is possibly neuroprotective through an effect on *[gamma]*-amino-butyric-acid receptors [9•].

There is also clinical evidence that high plasma glucose concentrations are harmful for patients with neuronal injury. Studies in patients with severe brain trauma, subarachnoid hemorrhage and ischemic stroke have shown an association of hyperglycemia and an increased morbidity and mortality [2••,10,11,12•]. It is unclear, whether hyperglycemia merely reflects the severity of neuronal injury, or whether high plasma glucose concentrations themselves adversely affect outcome after brain injury. To address this question a prospectively planned sub-analysis of a large randomized, controlled trial investigated the effects of intensive insulin therapy (target plasma glucose concentration 80–110 mg/dl) on outcome after neuronal injury [13••]. In the intensive insulin therapy group similar cerebral perfusion pressures were achieved with less norepinephrine administration and a lower ICP was found. This coincided with fewer seizures and a trend for less diabetes insipidus in patients with controlled plasma glucose levels. More patients rehabilitated to a level of independent living and fewer patients died 12 months after hospital discharge (30% versus 51%). Due to a small sample size, however, these differences were not statistically significant. There was also a decrease of critical illness polyneuropathy in patients with intensively controlled glucose levels. The currently available evidence supports the implementation of intensive insulin therapy in patients with neuronal injury to prevent secondary brain damage. This type of study supported the concept of strictly controlling plasma glucose concentration in a range of 80–110 mg/dl by careful insulin therapy.

Anesthetics

The proposed mechanisms of neuroprotection by anesthetic agents include reduction of cerebral metabolism and ICP (with the exception of volatile anesthetics), suppression of seizures and sympathetic discharge, and a reset of the thermoregulatory threshold. Additionally, anesthetics may reduce intracellular calcium and free radical accumulation [14•] or inhibit glutamate toxicity [15•]. In the absence of clinical outcome trials, however, the clinical value of these experimental data remains controversial.

Volatile anesthetics

Animal studies with focal or incomplete hemispheric ischemia have shown that isoflurane [16,17], sevoflurane [18], and desflurane [19] decrease infarct size and improve neurologic outcome when given prior to the ischemic challenge. It is questionable, however, whether the anti-necrotic effects of volatile anesthetics seen in these different ischemia models are permanent. As indicated above neurons may die from necrosis after severe injury, or by delayed neuronal death (apoptosis) if the tissue is exposed to a lesser degree of hypoxia or ischemia. Studies in rats subjected to focal cerebral ischemia have shown that necrotic cell death was

substantially reduced at 2 days in isoflurane anesthetized rats compared with awake controls [20]. At 14 days from ischemia, however, cortical and subcortical damage was not different between isoflurane and the awake state. In these studies the number of apoptotic cells increased with time, an effect that was blocked in the presence of caspase-3 inhibition [21•,22•]. This questions the sustained neuroprotective effects of volatile anesthetics and strengthens the requirement for long-term rather than short-term experimental outcome studies on neuroprotection.

The volatile anesthetic xenon reduces glutamate, *[alpha]*-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainite-induced membrane currents [15•]. After oxygen deprivation *N*-methyl-D-aspartate (NMDA) or glutamate exposure of cultured neurons and glia cells xenon reduced neuronal damage at sub-anesthetic concentrations [23]. In rats subjected to cardiopulmonary bypass neurological function was significantly better (Morris Water Maze) in the presence of xenon until day 12 but without differences in hippocampal damage [24]. These results indicate that xenon has neuroprotective potential.

In contrast to the experimental evidence indicated above, the neuroprotective properties of volatile anesthetics have not been proven in any clinical settings, such as in patients with traumatic brain injury or stroke.

Hypnotics

Propofol and barbiturates reduce ICP by suppression of metabolism, and thereby lowering CBF and intracranial blood volume. Additionally, hypnotics might extend the ischemic tolerance of neurons. In rats subjected to focal cerebral ischemia using endothelin injection infarct volume was reduced by propofol infusion at 3 days, but not 3 weeks from injury [25•] although functional performance was still better. This is consistent with the experimental evidence for volatile anesthetics from which the ischemia model itself and the duration of postischemic observation seem to make a difference in outcome. For example, in a rat model of incomplete hemispheric cerebral ischemia (a mild to moderate injury) propofol reduced histopathological damage and enhanced anti-apoptotic processes at 4 weeks after injury [26•]. This suggests that the severity of permanent focal ischemia is beyond the anesthetic potential to block necrosis and apoptosis. Anesthetics provided sustained neuroprotection, however, in the presence of low flow ischemic states.

The imidazole derivative etomidate has similar pharmacodynamic characteristics to barbiturates and propofol. Etomidate increased infarct size, however, following experimental focal cerebral ischemia, compared with isoflurane or thiopental [27], possibly because imidazoles further decrease microcirculation in tissue undergoing periinfarct depolarizations by inhibition of nitric oxide synthase [28•].

In summary, anesthetic agents seem to exert neuroprotective action during mild to moderate ischemia in animals, but fail to produce sustained neuroprotection with more severe ischemic insults [29••].

Magnesium

Magnesium reduces infarct volume in various animal models of embolic stroke with a time window of up to 6–12 h. The mechanisms by which magnesium protects include the reduction of

presynaptic release of glutamate, blockade of NMDA-receptors, smooth muscle relaxation (improved perfusion), suppression of cortical spreading depression, improvement of mitochondrial calcium buffering, and blockage of calcium entry via voltage-gated channels. In several small pilot trials magnesium decreased the proportion of dead or disabled patients after stroke. In contrast, the results of the Intravenous Magnesium Efficacy in Stroke (IMAGES) trial with 2589 patients showed that magnesium (16 mmol intravenous magnesium sulphate over 15 min and then 65 mmol over 24 h) given within 12 h from acute stroke did not reduce the risk of poor outcome at 90 days [30••]. Furthermore, mortality was slightly higher in the magnesium treatment group. A planned subgroup analysis, however, showed benefit of magnesium in non-cortical stroke. The majority of patients received medication beyond a 6-h window but only 3% of patients were treated within 3 h of symptom onset. As this may explain the loss of effectiveness of magnesium therapy an ultra-early infusion of magnesium is currently being tested in the Field Administration of Stroke Therapy Magnesium (FAST-MAG) trial. The published FAST-MAG pilot trial data showed that paramedic initiated infusion is safe and feasible and that the infusion time point is reduced to 26 min after onset [31•]. In contrast to results in ischemic stroke, the application of magnesium sulfate in aneurysmal subarachnoid hemorrhage (MASH trial) in 283 patients (initiated 4 days after subarachnoidal hemorrhage and continued for 14 days) reduced the risk of delayed cerebral ischemia by 34% and the risk for poor outcome after 3 months by 23% [32••]. An international phase III trial is therefore planned to validate these results. These data indicate that brain protection from magnesium relates to the time of treatment initiation and to the type of cerebral ischemia.

Osmodiuretics

Elevated ICP after cerebral insults is associated with increased morbidity and mortality. Rapid infusion of osmodiuretics is the recommended first-line treatment to decrease high ICP and, thereby, increase cerebral perfusion pressure, which results in improved microcirculatory blood flow in laboratory animals and humans. This effect is related to plasma expansion with consecutive reduction in hematocrit, plasma viscosity, and cerebral blood volume as well as mobilization of extracellular fluids along the osmotic gradient.

In the last years several osmodiuretics have been investigated. In patients after subarachnoid hemorrhage or head trauma 7.2% hypertonic saline in 6% hydroxyethyl starch or 7.5% saline in combination with 6% dextran-70 solution (HSD) reduced elevated ICP [33••,34••]. The ICP-decreasing effects of HSD seemed to be more effective than 20% mannitol [34••]. Ultra-early high-dose mannitol administration (1.4 g/kg) in the emergency room reverses recent clinical signs of impending brain death in head-trauma patients (Glasgow Coma Scale, 3; bilateral abnormal papillary widening) and improved outcome after 6 months in comparison with normal concentrations of mannitol (0.7 g/kg) [35••]. In conclusion, the intermittent administration of osmodiuretics is an effective and safe therapy for intracranial hypertension after neuronal injury.

Glucocorticoids

The proposed mechanisms by which glucocorticoids reduce neuronal injury include increased order of lipid bilayers, free radical scavenging, reduction of cerebral edema and anti-inflammatory processes, and prevention of free fatty acid accumulation by inhibition of lipidperoxidation. Studies in patients with acute stroke or following cardiac arrest, however, were unable to demonstrate a significant reduction in infarct size or improvement in neurologic

outcome with the infusion of glucocorticoids (e.g. dexamethasone, methylprednisolone) despite promising experimental studies.

In a randomized prospective trial including 20 000 patients with head injury the effect of methyprednisolone (loading dose, 2.0 g in 1 h; infusion, 0.4 g/h for 48 h) on outcome was investigated. The study was terminated after inclusion of 10 008 patients, because methyprednisolone increased mortality 2 weeks and 6 months after trauma [36••,37•]. Unfortunately, plasma glucose concentration was not controlled during the study. Additionally, patients might have suffered from secondary adrenal insufficiency after methylprednisolone was terminated. In conclusion the routine administration of methylprednisolone after head injury cannot be recommended.

Statins

Besides inhibition of cholesterol synthesis, statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) may increase the endothelial nitric oxide concentration, reduce oxidative stress, possess anti-inflammatory effects, and contribute to plaque stabilization [38]. In rats subjected to permanent focal cerebral ischemia administration of simvastatin increased the endothelial nitric oxide synthase immunoreactivity and reduced infarct volume after injury [39]. Surprisingly, reduction of infarct volume by statin treatment was even greater at later time points and initiation of statins after cerebral ischemia resulted in reduction of stroke size similar to that observed with prophylactic treatment. In contrast, only prophylactic but not delayed administration of simvastatin improved functional outcome in neonatal rat stroke [40].

The preventive effects of statins have been shown in several clinical trials. In 20 536 patients with cardiovascular diseases or other high-risk conditions simvastatin (40 mg/day) reduced the rate for ischemic stroke by 28% [41••]. After aneurysmal subarachnoid hemorrhage or stroke a preexisting medication with statins improved functional outcome and showed a significant lower incidence of delayed cerebral ischemia [42•,43••]. Therefore, treatment with statins in patients with a high risk for cardiovascular diseases is possibly justified.

The protective effects of statin medication after ischemic stroke (40 mg simvastatin from day 7 and 20 mg until day 90) was tested in 60 patients in the Markers of Inflammation after Simvastatin in Ischemic Cortical Stroke (MISTICS) trial. In preliminary results simvastatin significantly improves National Institutes of Health Stroke Survey scores at day 90. Final answers should come from the Fast Assessment of Stroke and Transient Ischemic Attack to Prevent Early Recurrence (FASTER) trial, which was initiated in 2003 to evaluate the efficacy of immediate treatment of 7500 patients with a combination of antiplatelet therapy (clopidogrel) or statins (simvastatin) therapy within 24 h of onset of minor stroke or transient ischemic attacks.

Although clinical data indicate effective prevention of stroke by statins (risk reduction), the use of statins or combination with antiplatelet drugs in response to cerebral ischemia requires further characterization.

Conclusion

Avoidance of acute physiologic derangements (i.e. control of physiological variables) is the best neuroprotective strategy after neuronal injury. These include, amongst others, therapy for fever and hyperglycemia or hypoglycemia (target 80–110 mg/dl). Furthermore, anesthetics given prior to mild or moderate ischemic challenges in rats appear to extend the ischemic

tolerance of neurons but clinical trials are lacking. The neuroprotective property of xenon needs further evaluation. Magnesium seems to be an effective neuroprotectant in patients with subarachnoid hemorrhage. Statins given prophylactically and chronically reduce the incidence of stroke. The acute neuroprotective property of statins, however, needs further investigation. Routine application of glucocorticoids is not indicated in the treatment of patients with head injury.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

•• of outstanding interest

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2•• Claassen J, Vu A, Kreiter KT, *et al*. Effect of acute physiologic derangements on outcome after subarachnoid hemorrhage. Crit Care Med 2004; 32:832–838. **Ovid Full Text** **Bibliographic Links** This study determined the effect of acute physiologic derangement on outcome after subarachnoid hemorrhage. Furthermore, a physiologic derangement score was designed. [Context Link]

3•• Holzer M, Bernard SA, Hachimi-Idrissi S, *et al*. Hypothermia for neuroprotection after cardiac arrest: systematic review and individual patient data meta-analysis. Crit Care Med 2005; 33:414–418. **Ovid Full Text** **Bibliographic Links** This is an excellent review and individual meta-analysis to assess whether induced hypothermia improves neurologic recovery in survivors of primary cardiac arrest. [Context Link]

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6•• Todd MM, Hindman BJ, Clarke WR, Torner JC. Mild intraoperative hypothermia during surgery for intracranial aneurysm. N Engl J Med 2005; 352:135–145. **Ovid Full Text** **Bibliographic Links** This randomized trial at 30 centers determined the effect of intraoperative cooling during open craniotomy for intracranial aneurysm surgery. [Context Link]

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15• Dinse A, Fohr KJ, Georgieff M, *et al*. Xenon reduces glutamate-, AMPA-, and kainate-induced membrane currents in cortical neurones. Br J Anaesth 2005; 94:479–485. **Bibliographic Links** | This study in cortical neurons investigated the effects of xenon on excitotoxic receptors. [Context Link]

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Keywords: anesthetics; corticosteroids; hyperglycemia; hypothermia; magnesium; neuroprotection; osmodiuretics; statins

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