The treatment of ischemic brain disease remains a challenge. There is as yet no clinical evidence that any commonly used agent affords significant neuroprotection against ischemic injury. However, a large volume of experimental data shows that anaesthetics do have at least have short term neuroprotective properties in vitro as well as in vivo in animals. This article will commence with a brief summary of the main changes in brain metabolism, triggered by ischemic/anoxic injury and neuronal death. I will then review some experimental data showing that anaesthetics exhibit neuroprotective properties both in vitro and in vivo. Finally, I will discuss the clinical relevance of these findings and the prospects for the future.

**Pathophysiology of Hypoxia, Ischemia and Neuronal Death.**

Considerable progress has been made in the understanding of the consequences of brain anoxia/ischemia on metabolism and neuronal viability [1]. Impairment of the blood and/or oxygen supply to the brain reduces ATP production and affects energy-dependent processes such as the Na/K/ATPase transporter. Activation of ATP-dependent K channels and calcium-activated K channels is interrupted, leading to initial neuronal hyperpolarization and electrical silence just after the onset of ischemia. The loss of potassium transport leads to its accumulation outside the neurons and subsequent slow depolarization. Once a threshold is reached, depolarisation leads to the complete loss of the membrane potential, with massive Na and Ca entry into the cell. The release of excitotoxic amounts of glutamate from nerve terminals is triggered, activating both NMDA and AMPA receptors. This enhances Na and Ca entry and K extrusion from the neurons through the glutamate receptor-coupled cationic channels.

During ischemia, cytosolic Ca concentrations increase markedly, due to activation of both NMDA receptors and voltage-gated Ca Channels, but also due to the blockade of the Na/Ca transporter and the release of Ca from intracellular stores. The increase in cytosolic Ca plays a prominent role in the development of ischemic injury and neuronal death by necrosis and/or apoptosis, by producing free radicals, DNA damage and proteolysis. Necrosis consists of cell disintegration, which spreads to adjacent neurons. Apoptosis is a physiological process for eliminating neurons during embryonic development. During cerebral ischemia, apoptosis is triggered as an actively programmed cell death; in contrast to necrosis, it does not damage adjacent neurons. It is thought to be initiated by the release of cytochrome C from the mitochondria, producing ATP when oxygen is available. This leads to activation of caspases and programmed cell death. Apoptosis is tightly regulated by both anti-apoptotic factors (bcl-2) and pro-apoptotic ones (bax, bad). Tyrosine phosphorylation, triggered by growth factors (NGF, BDNF), plays a major role in the inhibition of neuronal apoptosis.

**Neuroprotective Effects of Anaesthetics.**

**Local anaesthetics.**

The first step in the ischemic cascade is influx of sodium; prevention or reduction of this offers a mechanism for neuroprotection. The ability of anaesthetics to block the hypoxia-induced changes in Na+ influx, rather than blocking propagation of action potential, predicts their neuroprotective effects. Lidocaine blocks the voltage-gated Na channels and protects the brain against ischemic damage. In rat hippocampal slices subjected to 10 min anoxia, low concentrations of lidocaine and tetrodotoxin improve recovery of CA1 pyramidal cells, by reducing Na influx and depolarisation. Higher concentrations can partially restore ATP production and also block the increase in Na and depolarization induced by hypoxia, but do not block neuronal activity during normoxic conditions [2]. An antiarrhythmic dose of lidocaine, given before, during or after transient focal cerebral ischemia, significantly reduces infarct size and improves neurological outcome [1,3]. Blocking apoptotic cell death in the penumbra involving cytochrome C release and caspase 3 activation may also play a role in these effects. Interestingly, lidocaine possesses neuroprotective effects in cardiac surgical patients. Mitchell et al found a better outcome in patients undergoing mitral and aortic valve surgery, while Wang et al observed improved early cognitive recovery in CABG patients [4]. Cognitive decline is associated with the occurrence of silent brain infarcts [5]. There is thus both experimental and clinical evidence to suggest that lidocaine may be neuroprotective in cardiac surgical patients.
INTRA VENOUS ANAESTHETICS.

Barbiturates such as pentobarbital and thiopental improve recovery of brain slice CA1 pyramidal cells from hypoxia. Thiopental attenuates the electrophysiological, biochemical and morphological changes of hypoxia in rat hippocampal slice CA1 pyramidal cells [1]. These agents also reduce the magnitude of damage induced by temporary focal cerebral ischemia, although the mechanisms are unclear. They may involve reduced glutamate excitotoxicity, sodium channel blockade, enhanced GABA receptor inhibition, depression of Ca entry into the neurone, or reduction in free radical production [6]. Some of these mechanisms, particularly the first, may also account for the protective effect of hypothermia.

Pre-ischemic ATP content does not influence post-ischemic recovery from anoxia [7]. However, high doses of barbiturates may exert an immunodepressant effect by inhibiting nκB, which, together with their negative hemodynamic effects, may limit efficacy in vivo [8]. Thus there is no convincing evidence to suggest that thiopental is clinically effective in protecting the brain against ischemic injury. In neurosurgical patients with intracranial hypertension, thiopental may usefully reduce cerebral blood flow and decreasing CMRO2. However cardiovascular depression and prolonged emergence from anaesthesia reduce the practical potential of barbiturates. Nevertheless, barbiturate therapy has been advocated in neurosurgical patients undergoing occlusion of intracerebral vessels > 10 min.

Propofol, like barbiturates, reduces CMRO2 and cerebral blood flow, but its ability to protect the brain against ischemic injury remains controversial. It does not improve recovery of CA1 pyramidal cells from hypoxia, or significantly attenuate NMDA- and AMPA-induced excitotoxicity in vitro. [9]. However, it may improve the recovery of cultured cortical neurons subjected to a 90 min oxygen-glucose deprivation followed by reperfusion. The mechanisms involved are likely to be the restoration of glutamate uptake, independent of the glial transporter GLT1. [10]

Etomidate also reduces cerebral metabolism. It reduces glutamate and dopamine release during cerebral ischemia, but no neuroprotective effect has been demonstrated. Ketamine, a non-competitive NMDA receptor antagonist, exhibits potent neuroprotection in numerous animal models both in vitro and in vivo. Unfortunately, like other NMDA receptor antagonists, it may also exhibit neurotoxic actions, and there is no evidence to support its use clinically. Remacemide, however, another NMDA, may offer some degree of clinical cerebral protection.

VOLATILE ANESTHETICS

Nitrous oxide may be detrimental in ischemic brain injury. Like the other NMDA receptor antagonists, MK801 and ketamine, it has a neurotoxic effect, a phenomenon possibly particularly critical in the perinatal period [11]. Prolonged exposure to nitrous oxide also produces cell death in cortical neurons of the adult rat brain. This effect can be prevented by co-administration of GABA-receptor agonists, such as benzodiazepines [12]. Taken together with its effect on cerebral blood flow, CMRO2 and intracranial pressure, the use nitrous oxide cannot be recommended in ischemic injury.

Xenon is a short acting, well tolerated NMDA receptor antagonist which exhibits neuroprotective properties, both in vitro and in vivo, where ketamine, nitrous oxide and MK-801 produce neurotoxicity. It protects the brain during focal transient ischemia in mice [13]. The neuroprotective effects against anoxic injury are synergistic with those of isoflurane in a neuronal-glial coculture model [14]. Thus xenon offers some promise, but more research is needed to clarify its effects on cerebral metabolism and hemodynamics in humans.

Volatile anesthetics (isoflurane, sevoflurane and desflurane) all exhibit in vitro and in vivo neuroprotective properties in experimental models, via a reduction in pre- and postsynaptic glutamate excitotoxicity [15-19]. In rat hippocampus slice experiments, isoflurane has neuroprotective effects at 7 and 15 days after exposure to ischemic injury. In dogs subjected to circulatory arrest, isoflurane reduces hippocampal neuronal loss. Preconditioning with isoflurane protects against ischemia induced by occlusion of the middle cerebral artery, an effect which depends on the activity of ATP-dependent glibenclamide-sensitive K+ channels. Thus the in vitro beneficial effects of isoflurane may be observed weeks after the insult. Protection against myocardial infarction achieved by preconditioning has been extensively reported for volatile anaesthetics both experimentally and clinically. If the preconditioning effects of volatile anaesthetics also apply to the brain, this could be of great interest in high-risk surgery such as cardiac surgery, but remains to be investigated.

THERAPEUTIC PERSPECTIVES FOR PREVENTION AND TREATMENT OF ISCHEMIC BRAIN INJURY IN THE
PERIOPERATIVE CONTEXT.

To date, large trials attempting to demonstrate pharmacological neuroprotection have produced disappointingly small reductions in morbidity and mortality. He reasons for this may include lack of convincing experimental data, underpowered clinical trials, heterogeneity of patients, timing of drug administration, and the difficulty in getting the agent to the ischemic zone [20]. Some of these considerations also apply to anaesthetics given perioperatively. The neuroprotective efficacy of volatile anaesthetics is crucially affected by their actions on cerebral blood flow, intracranial pressure and CMRO2; their cerebral vasodilator effects preclude their use in patients with severe intracranial hypertension. Thus, even though they exhibit possibly substantial neuroprotective properties in vitro (e.g. by decreasing glutamate excitotoxicity), they are ruled out for many emergency neurosurgical or neuroradiological procedures. Further, their actions on the reperfusion phase and on free radical production also require further investigation.

However, anaesthetics may protect against brain ischemia in some clinical situations. During cardiac surgery, lidocaine may protect against the neurocognitive sequelae of micro embolisation. Volatile anaesthetics, administered before starting cardiopulmonary bypass, may exert preconditioning effects and thus improve postoperative neurological outcome. Xenon, which is well-tolerated, may offer neuroprotection. Its effects however, on cerebral hemodynamics, remain to be clarified. The use of these anaesthetics and/or other agents (human albumin, erythropoïetin) or prophylactic mild hypothermia might contribute to reduce the incidence of ischemic injury in high-risk perioperative situations.

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