Prevention and Treatment of Secondary Brain Damage
Clinical Aspects
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In acute cerebral lesions, primary and secondary brain damage can be distinguished. This is of utmost clinical importance since the primary damage cannot be prevented, but secondary damage might be prevented. The concept of primary and secondary brain damage has been introduced by neuropathologists and neurosurgeons decades ago.1,4 Livingston and Nouruzadeh1 stressed that the outcome of severe cerebral lesion does not depend only on the primary damage, but also on the extent of secondary lesions.

In severe head injury the primary damage comprises hemorrhagic contusions, cerebrovascular lesions, and lesions of the nerve fibers, now called "diffuse axonal injury."3,4 In focal cerebral ischemia, the focal necrosis represents the primary lesion.

Secondary brain damage may have intracranial and extracranial causes. The most important extracranial causes following a severe head injury are hypoxia because of respiratory insufficiency and arterial hypotension. Patients with severe head injuries are often polytraumatized and in shock. Both hypoxia and hypotension may lead to secondary cerebral ischemia.

The most important intracranial causes for secondary brain damage are hemorrhage and edema leading to increased intracranial pressure and causing brain shift and distortion. Finally, there is secondary ischemic brain damage as well. So far, the best treatment of acute cerebral lesions, such as severe head injury and ischemia, is to prevent secondary brain damage.

This article will discuss two important aspects of secondary brain damage: posttraumatic hypoxia and the possible role of mediator compounds of brain edema. While prevention of posttraumatic hypoxia is presently a goal in the prevention and treatment of secondary brain damage, interaction of putative mediators is not yet a clinical reality. For further information on secondary brain damage, recent reviews on this topic are recommended.3,4

Secondary Brain Damage by Posttraumatic Hypoxia

There is agreement that posttraumatic hypoxia is an important cause of secondary brain damage since patients with posttraumatic hypoxia do much worse compared to patients without this complication.1,4 It had been speculated that hypoxia caused secondary ischemia, though the exact mechanisms were not clear until recently. With the advent of phosphorous magnetic resonance spectroscopy it became feasible to study cerebral energy metabolism noninvasively and sequentially following brain injury. The 31P-NMR-spectroscopy allows monitoring tissue pH as well as the tissue concentrations of phosphocreatine and ATP. These parameters were studied in cats subjected to a fluid percussion brain injury.6,7 This trauma model imitates a severe brainstem contusion with diffuse alterations in the supratentorial compartment, a special type of severe brain injury which is also often seen under clinical conditions. The spectroscopic studies were combined with microsphere measurements of cerebral blood flow and determinations of oxygen and glucose consumption.

The animals were randomized to three experimental groups. Eight animals were ventilated normally during and following trauma. A second group was hypoventilated, but did not receive trauma, and in a third group trauma and hyperventilation were combined. Hypoventilation was defined as 90 s of apnea followed by 30 min of hyperventilation to a PaO2 of 35–40 mm Hg. After this period, normal ventilation was restored, and the animals were monitored for 8 h after trauma.10

Tissue pH, cerebral blood flow and the cerebral metabolic rate of glucose in the three experimental groups are shown in Figure 1. Whereas in traumatized as well as in animals only hypoventilated but not traumatized tissue pH was not significantly altered during the experimental period, marked and significant tissue acidosis was observed in animals who were traumatized and received the secondary insult, i.e.,

Aim of Treatment

Control of ICP and CPP

- Surgical
- Non-Surgical
- Pharmacological
  - CSF drainage
  - Head elevation
  - Dehydration
  - Decompression
  - Hyperventilation
  - Barbiturates
  - Blood pressure

Figure 1. Tissue pH, cerebral blood flow, and cerebral metabolic rate of glucose in three experimental groups of cats (fluid percussion brain injury, hypoventilation, and traumatized and hypoventilated animals). The combination of brain injury and hypoxia leads to tissue acidosis because of inadequately increased blood flow and a shift to anaerobic glycolysis (modified after references 10 and 11).
hypoventilation. However, soon after restoration of normoventilation, tissue acidosis disappeared. During the period of hypoventilation, untraumatized animals revealed a 6-fold increase in CBF, while CBF was only increased to 250% of control values in animals with trauma and hypoxia. Furthermore, increased glucose consumption and decreased tissue concentration of phosphocreatine during the period of posttraumatic hypoxia clearly demonstrated that during posttraumatic hypoxia CBF cannot be increased to the actual tissue demand. There is a shift to anaerobic glycolysis, the tissue becomes acidic, and there is a decrease of high-energy phosphates indicating an insufficient perfusion of the brain. There is no question that this is severe secondary brain damage. Comparative findings were obtained for the combination of cerebral trauma and arterial hypotension.

The clinical implications are obvious: after severe brain injury, hypoxia and hypotension must be prevented, or counteracted as soon as possible. Resuscitation, ie, intuba-
tion, ventilation and restoration of normal blood pressure, should start at the site of the accident.

**Intracranial Causes for Secondary Brain Damage**

The most important intracranial causes for secondary brain damage are hemorrhage and edema leading to an increased intracranial pressure and causing brain shift and distortion. Finally, there is also secondary ischemic brain damage.

How can we prevent or treat these complications? It is obvious that space-occupying hematomas have to be evacuated as soon as possible. In treatment of brain edema, all measures now in use are based on symptoms. The aim of treatment is to control intracranial pressure and, as important, cerebral perfusion pressure. There are a number of different possibilities to reduce intracranial pressure or to secure cerebral perfusion pressure (Fig. 2). Surgical interventions are CSF drainage or decompression. Nonsurgical measures are moderate head elevation, mild hypotension, and a controlled increase or decrease of blood pressure. Dehydration by infusion of hyperosmolar mannitol and furosemide are the most important pharmacological interventions against an increased ICP. The induction of barbiturate coma is regarded as the ultimate procedure to reduce ICP.

It is easy to recognize that really not much has changed recently in prevention or treatment of secondary brain damage. There are, however, some promising new avenues to treat secondary brain damage more specifically. This leads to the topic of mediators of secondary brain damage and their mechanisms.**

There are a number of substances which are released following brain insults, which are harmful to the brain and where specific inhibition could result in less damage. Putative mediators of secondary brain damage are arachidonic acid, prostaglandins, leukotrienes, free radicals, kinins, the excitotoxic amino acid glutamate and others. Mechanisms by which these mediators exert secondary brain damage include enhancement of blood-brain barrier damage, microvascular disturbances, cytotoxic edema, cell necrosis and impairment of nervous functions. In this context, the levels of evidence for the role of some interesting mediator compounds can only briefly be reviewed. The most interesting candidates are kinins, the active compounds of the kallikrein-kinin system, the amino acid glutamate and arachidonic acid. It has been shown that these substances induce damage to the brain. Kinins alter blood-brain barrier function, i.e., increase the cerebrovascular permeability, arachidonic acid acts neurotoxically and opens the blood-brain barrier, while glutamate causes cytotoxic cell swelling and finally cell necrosis.8,7,15 All of these systems are activated after various cerebral insults. Finally, it could be demonstrated that specific therapeutic inhibition of these three systems resulted in less damage. Therapeutic inhibition, though, is on an experimental level so far.8,7,15

It has to be pointed out that there is certainly not just one important mediator of secondary brain damage. There are complex and intimate relationships of mediator systems, such as interactions of arachidonic acid, its metabolites, the kallikrein-kinin system and platelet activating factor. Therefore, effective therapeutic inhibition can probably be achieved only if there is inhibition of different systems at different levels.

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**REFERENCES**


