Exp Toxic Pathol 1999; **51**: 143–150
URBAN & FISCHER

[1]Institute of Pathophysiology, [2]Department of Anesthesiology and Intensive Care, Friedrich Schiller University, Jena, Germany

Ontogenetic aspects of traumatic brain edema – facts and suggestions*

REINHARD BAUER[1], BERND WALTER[1], HARALD FRITZ[2], and ULRICH ZWIENER[1]

Address for correspondence: Dr. REINHARD BAUER, Institute of Pathophysiology, Friedrich Schiller University, D-07740 Jena, Germany; Phone: +49 (03641) 938956; Fax: +49 (03641) 938954; e-mail: rbau@mti-n.uni-jena.de

Key words: Brain edema, pathogenesis; Brain development; Blood-brain barrier; Traumatic brain edema; Edema, brain.

Summary

Diffuse brain swelling (DBS) after severe traumatic brain injury (TBI) occurs more commonly in children than adults. Most of the recent clinical studies suggest that young children are more negatively affected by DBS. Until now studies in young animals in which the pathophysiology of DBS was evaluated remained seldom. However, pathogenetic mechanisms of edema formation after TBI in the immature brain appeared to be different in comparison to adult brains. There are evidences that vasogenic as well as cytotoxic edema components may be responsible for the development of DBS. Besides mechanical disturbance, the blood-brain barrier seems to be strongly endangered by oxidative stress after TBI because regional antioxidative capacity is obviously diminished. In addition, cytotoxic components of DBS may be caused by at least two different mechanisms. First, it was shown that a sustained posttraumatic cerebral hypoperfusion occurs in the immature brain. Moreover, a transient increase of NMDA receptor expression at this period of life may be responsible for an increased threat of intracellular sodium ion accumulation in brain cells. Obviously, brain swelling can be detrimental because it can elevate intracranial pressure, impair CBF, and may represent ongoing secondary brain injury.

Introduction

Diffuse brain swelling (DBS) occurs after traumatic brain injury (TBI) more often in children than adults (BRUCE et al. 1981; ALDRICH et al. 1992), and children found to have DBS have a threefold higher mortality rate than those without it (ALDRICH et al. 1992). Recent studies clearly revealed that age has an impact on severity and sequelea of TBI (ADELSON and KOCHANEK 1998). Mortality rate is particularly high in the subgroup of children less than four years of age (LUERSSEN et al. 1988). Moreover, functional sequelea are more pronounced in younger children (LEVIN et al. 1992; DUHAIME et al. 1996). However, differentiation of underlying mechanisms of injury including brain swelling and functional responses at different stages of brain maturity is indispensable for a better understanding of this complex pathogenesis of TBI.

Development of blood-brain barrier

The concept of a barrier between the blood and the brain arose in the late 19th century when the German bacteriologist PAUL EHRLICH observed that certain dyes, e.g., a series of aniline derivates, administered intravenously to small animals stained all the organs except the brain. EHRLICH'S interpretation of his result was that the brain had a lower affinity for the dye than the other tissues. In the late 1960's the hypothesis that brain capillaries provide the anatomical basis of the blood-brain barrier (BBB) could be confirmed using electron microscopy. The brain capillary is a structural unit that consists of endothelial cells, pericytes, and an associated basement membrane surrounded by foot processes of adjacent astrocytes. There is clear evidence that most if not all, barrier properties reside in the endothelial cell. The BBB is present in all vertebrate brains and develops within the first trimester of human fetal life.

The different properties of the barrier are divided into the three categories of anatomic, metabolic, and carrier-mediated transport. These are involved in the maturation process that may accrue a special importance even in response to brain injuries like TBI. In contrast to peripheral capillaries, BBB capillaries have a low nonspecific permeability to polar substances because they are nonfene-

* supported by BMBF 01ZZ9602

strated and are interconnected by a continuous network of complex tight junctions that functionally fuse the plasma membranes of adjacent endothelial cells. Although tight junctions are found in the capillaries of all tissues, they are less extensive and complex in non-barrier-forming endothelia and contain intercellular clefts through which passive diffusion occurs. Such clefts are markedly diminished in mature brain capillaries.

During the late period of BBB maturation, i.e. at late fetal period and early postnatal life, endothelial junctions resemble adult-like junctions in their size and density, but approximately 20 % of the junctional clefts are enlarged. This is consistent with a paracellular channel (SCHULZE and FIRTH 1992). In regard to the chronological sequence of BBB maturation there are significant species differences which correspond with the timing of brain growth and differentiation relative to the time of birth (DOBBING 1968). Until now, the importance of such large junctional clefts has not been known with certainty. However, it is assumed that they are responsible for small solute permeability in capillaries (STEWART and HAYAKAWA 1987). In addition, blood-brain barrier formation is characterized by formation of the basement membrane which becomes reconizable at regions where a close endothelial-astrocytic contact has been developed. The perivascular consolidation and basement membrane formation is accompanied by a marked reduction of a factor of 30 in paracellular diffusion during the first 3 to 4 postnatal weeks in rats and mice. Moreover, in regard to possibly altered features of water and cation permeability due to mechanically injured brain tissue it has to be noted that large junctional clefts in brain capillaries were found in rats of 24 days of age (SCHULZE and FIRTH 1992).

Basic mechanisms of brain edema formation

As noted above, diffuse brain swelling is a common feature of traumatic brain injury in infants and younger children. The contribution of edema and blood volume toward brain swelling with resulting intracranial pressure (ICP) rise in cases of TBI remains a critical problem. Early outcome studies of severe TBI in children suggested that the diffuse brain swelling resulted from vasomotor paralysis, cerebrovascular dilation, and increased cerebral blood volume, but not from edema (BRUCE, ALAVI 1981). More recently, this concept has become into question.

Indeed, it remains unclear whether or not the mechanisms of hyperemia, edema, or ischemia are major factors leading to the resulting cerebral swelling seen in children (ALDRICH et al. 1992). However, there are now some experimental and clinical studies which indicate that brain maturity has a strong impact on the pathogenetic process of brain swelling and ICP increase due to traumatic brain injury. The following description will focus on such possible components in detail.

Cerebrovascular response - possible contribution to brain swelling after TBI

At present no studies have been done which investigate the influence of TBI on CBV in the immature brain of different ages. However, ARMSTEAD and KURTH (ARMSTEAD and KURTH 1994) have shown that different cerebral hemodynamic responses occur following fluid percussion (FP) brain injury in newborn and juvenile pigs. In a closed cranial window preparation a lateral FP brain injury of moderate extent was performed which resulted in an early and progressive constriction of pial arterioles and small arteries which was pronouncedly longer lasting in newborn animals. Cerebral blood flow was concomitantly reduced and reached its lowest values of the end of the posttraumatic observation period, i.e. 180 minutes after FP injury. A transient rise of ICP was also more pronounced in newborn pigs. Underlying mechanisms of this transient ICP increase remain unclear. An abrupt increase of ICP with simultaneous vasoconstriction suggest that the intracranial volume expansion may result from translocated fluid due to the fluid percussion device. Dixon and co-workers have shown that FP impact induces an epidural fluid movement between the skull and the dura starting from the trephine hole within about 15 miliseconds (DIXON et al. 1988). This corresponds smoothly with the provoked intracranial (subdural) pressure pulse course (WALTER et al. 1999). The amount of fluid translocation could be determined by dural stiffness and/or the intensity of attachment of the dura mater with the skull bone. However, vascular congestion could obviously not provide the increase in volume necessary to increase ICP under these conditions of progressively constricted cerebral vasculature. Recent preliminary clinical studies confirm this observation of early cerebral blood flow decrease following severe traumatic brain injury in infants and young children (ADELSON et al. 1997). Adelson and co-workers found that young children (< 24 months of age) are a particular high-risk group with early hypoperfusion after severe TBI. Therefore, during the early period following the TBI with early cerebral blood flow reduction a deficit of oxygen delivery may result in an ischemic metabolism with subsequent secondary effects on cerebral energy requirement and consequences for intracranial volume regulation. Later on (after 24 hours) cerebral blood flow increases with an apparent uncoupling of cerebral blood flow and cerebral oxidative metabolism since cerebral metabolic rate of oxygen ($CMRO_2$) remained low. This suggests a hyperemia. Post-traumatic hyperemia is more common in children (> 70 %) than in adults (46 %) (ADELSON and KOCHANEK 1998).

The effect of such hyperemic periods on intracranial pressure was observed in our studies during periods of severe asphyxia in intrauterine growth restricted newborn piglets (WALTER et al. 1998). We found a considerable transient ICP increase by about 40 mmHg as shown in figure 1 A. As expected a marked vasodilation occurs which concomitantly causes a strong cerebral blood flow in-

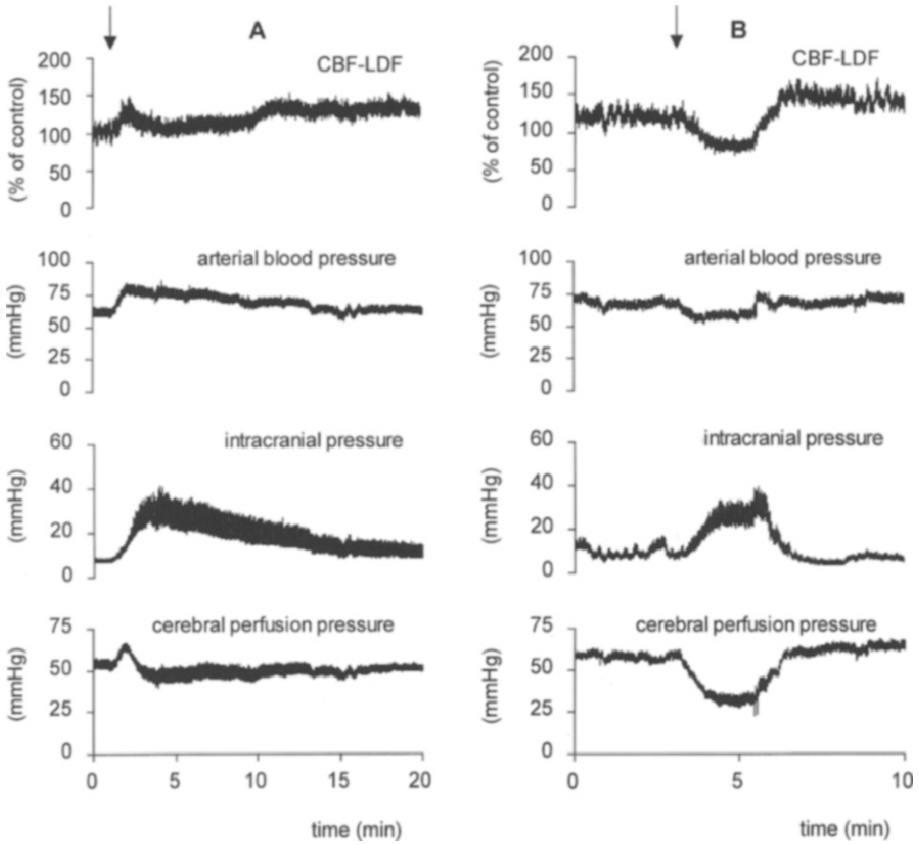

Fig. 1. Effects of hyperemic periods on intracranial pressure in an intrauterine growth restricted newborn piglet (25.5 hours old, b.w. 850 g) during the initial period of severe asphyxia (panel A; p_aO_2 = 21 mmHg, pCO_2 = 81 mmHg) and at recovery (panel B; p_aO_2 = 193 mmHg, pCO_2 = 41 mmHg) during a period of median nerve stimulation (in order to provoke somatosensory evoked potentials). Note a considerable transient increase of ICP by about 40 mmHg each. During initial asphyxia, a marked vasodilation occurs as expected which concomitantly causes a strong cerebral blood flow increase together with a moderate arterial blood pressure increase. The resulting cerebral perfusion pressure as the driving force of the brain perfusion was mainly maintained. This pattern reflects the effects of redistribution of the circulating blood due to severe hypoxemia and hypercapnia in favor of brain (here shown) , myocardium and adrenals and at the expenses of the other organs. However, a similar ICP increase may occur spontaneously or during a period of median nerve stimulation (in order to provoke somatosensory evoked potentials) in a compromised newborn brain as we have seen during the recovery period after 1hr severe asphyxia. Initiated by a moderate ABP decrease, a similar ICP increase (of about 40 mmHg) was accompanied by a moderate CBF decrease. Therefore, a marked CPP decline occurs which provokes cerebrovascular dilation obviously mediated by an activated but insufficent autoregulatory response.

crease together with a moderate arterial blood pressure increase. The resulting cerebral perfusion pressure as the driving force of the brain perfusion was widely maintained. However, a similar ICP increase may occur spontaneously or during a period of median nerve stimulation (in order to provoke somatosensory evoked potentials) in a compromised newborn brain as we have seen during the recovery period after 1hr of severe asphyxia (figure 1 B). In contrast to the early period of severe asphyxia that reflects the effects of redistribution of the circulating blood in favor of brain, myocardium and adrenals and at the expenses of the other organs, such a similar ICP increase is accompanied by a moderate CBF decrease. This response was preceded by an abrupt decrease in arterial blood pressure. Therefore, a marked decline in cerebral perfusion pressure occurs which provokes a cerebrovascular dilation obviously mediated by an activated but insufficient autoregulatory response. We assume that such periods of hypoperfusion accompanied by cerebrovascular congestion may be responsible for induction of secondary brain injury, i.e. ischemic intervals which may initiate or aggravate postasphyxtic or even posttraumatic brain edema formation.

Cytotoxic and neurotoxic and vasogenic components

Formation of traumatic brain edema is obviously a major cause of diffuse brain swelling (determined by CT findings) after traumatic brain injury. Studies in adult animals gave evidence that in an animal model which shows diffuse brain injury without focal brain lesions (impact-acceleration model (FODA and MARMAROU 1994)) the rise in ICP following severe trauma coupled with secondary insult (hypoxia and hypotension) was predominately

caused by cytotoxic edema and that ischemia plays a major role in the development of brain edema after this kind of head injury (ITO et al. 1996). Another type of brain injury with focal lesion and more or less widespread tissue alteration (Fluid percussion model) leads to temporary damage of the blood-brain barrier (vasogenic edema formation) which is further deteriorated due to periods of arterial hypertension (VAN DEN BRINK et al. 1994).

Which role the development of different types of cerebral edema plays in the pathophysiologic process associated with severe traumatic brain injury in the immature brain remains up to now widely unclear (ADELSON and KOCHANEK 1998). However, much information suggests that different periods of brain development may be distinctly prone to different types of intracerebral water accumulation due to traumatic injury. This will be now discussed in detail.

The key question is how short-term mechanical deformation of brain tissue is able to induce or maintain serious functional disturbances in microcirculation and volume regulation of neuronal cells, so that a progredient accumulation of water into brain tissue may occur? It could be shown that immediately after the primary traumatic impact a widespread neuronal depolarization occurs accompanied by a rise of the extracellular potassium ion ($[K^+]_e$) and glutamat concentration (FADEN et al. 1989; NILSSON et al. 1993; KATAYAMA et al. 1995). It is assumed that these processes represent the coupling between primary and secondary injury processes (KATAYAMA et al. 1995). Recent findings on cultured newborn rat neurons provide the electrophysiological substrate for that assumption. It could be demonstrated that a short-term (50 ms) sublethal cell stretch depolarized neuronal resting membrane potential by approximately 10 mV for about 24 h (TAVALIN et al. 1995). This delayed depolarization could be a prerequisite for initiation of increased brain water content, since such a pre-depolarisation could provide the condition to make repetitive depolarisation shifts possible which show similar features as observed at peri-infarct depolarisation shifts. Interestingly, initiation (but not maintenance) of this stretch-induced delayed depolarization requires neuronal firing, calcium entry, and N-methyl-D-aspartate receptor activation. The spreading depolarization shifts are the electrophysiological substrate of the steady potential breakdown of large neuronal and glial cell populations and also of smooth muscle cells and the endothelia of the affected microcirculation immediately after brain tissue compression, which is induced by excessive $[K^+]_e$ increase (> 60 mM) (NILSSON et al. 1993). Membrane depolarization results in serious disturbance of transmembraneous ion distribution with massive input of Ca^{2+} but also of Na^+, Cl^-, and water, according to the osmotic gradient which led to a concomitant cell swelling. One has to consider that this complex pattern of disturbances occur without energy failure.

The underlying mechanisms can be explained by the excitotoxic hypothesis of brain damage (SIESJÖ and BENGTSSON 1989). Depolarization induces a glutamate release with Ca^{2+} influx through an N-type voltage-sensitive calcium channel. The postsynaptic effects of glutamate occur on three receptors. Two of these are ionophoric receptors, which may be selectively activated by either α-amino-3-hydrox-5-methyl-4-isoxazole propionic acid (AMPA) or N-methyl-d-apartate (NMDA). The third is a metabotropic receptor, which is selectively activated by quisqualate and 1-aminocyclopentane-1S,3R-dicarboxylic acid (APCD). The AMPA receptor controls a channel that is permeable to monovalent cations (Na^+, K^+, and H^+), whereas the NMDA channel is also permeable to Ca^{2+}. The NMDA channel is normally blocked by Mg^{2+} in physiological concentrations, but this block is relieved when the membrane depolarizes. Because Na^+ influx through the AMPA channels leads to such depolarization, the simultaneous activation of both AMPA and NMDA receptors by glutamate is followed by depolarization and Ca^{2+} influx. Depolarization also allows Ca^{2+} influx through voltage-sensitive channels of the L and T type. The downhill inward flux of Ca^{2+} is normally balanced by an ATP-driven transport of Ca^{2+} out of the cell and by an electrogenic $3N^{a+}$- Ca^{2+} antiporter, which is energetically driven by the N^{a+} gradient and the membrane potential. These mechanisms may be disturbed in traumatically injured neurons, since short-term sublethal neuron stretch induced delayed depolarization is caused by an inhibition of the electrogenic ouabain-blockable Na^+ pump (TAVALIN et al. 1997). The disturbed Na^+ and Cl^- balance may impede K^+ re-uptake and in addition, because osmotically obligated water enters the cells, may cause the increased intracellular water content after TBI. The occurrence of spreading depolarization shifts after TBI were found in both gyrencephal (MAYEVSKY et al. 1996) and lissencephal brains (NILSSON et al. 1993; KATAYAMA et al. 1995; ROGATSKY et al. 1996). Recently, the potential importance of such repetitive spreading depolarization shifts in the pathogenesis of acute metabolic neuronal disturbances was impressively shown in regard to the maturation of an experimentally induced brain infarction due to focal brain ischemia (reviewed in OBRENOVITCH 1995; HOSSMANN 1996; GINSBERG 1997). Correspondingly, the progression of irreversible neuronal injury of the penumbra zone (SYMON et al. 1977; ASTRUP et al. 1981), the region immediately adjacent to a brain infarct with a reduced perfusion rate of 20 to 40 per cent (GINSBERG 1997), correlates strongly with sequence and severity of the peri-infarct depolarization shifts. The pre-existing balanced mismatch between metabolic delivery and demand, which maintains neuronal basal requirements in order to stabilize transmembrane ion disbalance, is disturbed largely, so that the possibility of impaired metabolic recovery increases for a increasing number of involved neurons and the probability of terminal depolarization and subsequent cell death strongly increases (HOSSMANN 1996).

Up until now, conditions of expansion of repetitive spreading depolarization shifts after traumatic brain in-

jury and also their pathogenetic importance has not been studied in the immature brain. However, some evidence exists that especially the immature brain shows functional pecularities which suggest that repetitive spreading depolarization shifts may easily occur due to traumatic brain injury and could provoke onset and also expansion of water accumulation within brain tissue. First, the immature brain is more susceptible to developing status epilepticus due to metabolic disturbances of different origin than the brain of a mature animal (MOSHE et al. 1983; SPERBER and MOSHE 1988). This has to do with a maturational imbalance between excitatory and inhibitory potentials. The GABAergic system as the predominant inhibitory neurotransmitter system in the brain shows a delayed development, since in neonates and rodents the binding sites for GABA are present at relatively low concentrations at birth and increase slowly in the postnatal period (JOHNSTON and SILVERSTEIN 1998). In contrast, glutamate receptors as the major excitatory ones (i.e. NMDA receptors) exhibit a peak in their expression during postnatal brain development (D'SOUZA et al. 1992; SLATER et al. 1993). Activation of these receptors is able to induce excessive ion fluxes, which predominantly lead to an intracellular overload of Ca^{2+} and Na^{+} ions. As pointed out earlier in detail, neuronal overload with Ca^{2+} activates proteases and phospholipases which may result in a loss of neuronal membrane integrity, disrupture of key cell functions and cell death. On the other hand, intracellular sodium ion overload connected with water influx caused cell swelling and thus when widespread, a cytotoxic brain edema (SIESJO 1993). Indeed, after local injection of *N*-methyl-d-apartate (NMDA) into the striatum of eight-day-old rats a fast and widespread appearance of intracellular water accumulation occurs (within 15 minutes). In contrast, in adult rats such a NMDA-induced cytotoxic brain edema only appears at the location of drug injection (VERHEUL et al. 1993). Moreover, in a subsequent study it was shown that the early diffusion changes were accompanied by only mild changes in the overall metabolic status as measured by in vivo ^{1}H magnet resonance spectroscopy (MRS) and ^{31}P MRS and metabolic imaging of brain sections. Minimal decreases in the high-energy phosphate levels and a small hemispheric acidosis were observed in the first 6 h after NMDA administration. In addition, there was very modest lactate accumulation. Twenty-four hours after the induction of the excitotoxic injury the tissue energy status was still only moderately affected, whereas an overall decrease of ^{1}H MRS-detected brain metabolites was found (DIJKHUIZEN et al. 1996).

The suggestion that excitatory amino acids (EAA; i.e. glutamate, aspartate) are involved in the pathophysiological sequelae of brain injury in adults has been proved by studies using both different experimental brain trauma models (FADEN et al. 1989; PALMER et al. 1993) and microdialysis in patients suffering from severe head injury (ZAUNER et al. 1996). Both showed an acute and marked increase in EAAs following trauma, which was related to the severity of the injury. Thus, provided that traumatic brain injury induced a respective increase of extracellular EAAs also in the immature brain, one can assume that under these conditions a widespead, NMDA-mediated intracellular water accumulation may occur which could be one component of early diffuse brain swelling after TBI.

Apart from disruptions of cerebral vessels due to the mechanical impact and the related effects of subsequent bleedings, microvascular alteration and therefore an injuried blood-brain barrier is also of great significance for the genesis of traumatic brain edema. However, up until now it has been widely unclear, how the initiation of a BBB leakage appears due to short-term mechanical alteration. It is obvious that vascular ruptures and extravasation of blood-derived substances like thrombine, thromboxane from platelets, and others may induce local microvascular disturbances predominantly through local ischemia and subsequent endothelial injury leading to focal leakage where protein-rich blood plasma may emanate into the brain extracellular compartment and a vasogenic edema may develop. Moreover, the increase in BBB permeability appears to be at least in part mediated by autacoids (i.e. bradykinin, histamine, arachnoid acid, and nitrous oxide) released from injuried brain tissue (SCHILLING and WAHL 1997). However these compounds may rather be connected with processes of secondary aggravation of an ongoing formation of a vasogenic edema because most of the experimental findings are derived from adult animal models with primary disturbance of the BBB (i.e., cold lesion-induced brain edema) and the generation of relevant amounts of respective autacoids dependents on kininogen uptake from the plasma (bradykinin (MAIER HAUFF et al. 1984)), activating blood-born mast cells (histamine (ORR and PACE 1984)), or may be mediated by polymorphonuclear leukocytes (arachidonic acid (UNTERBERG et al. 1984)).

Widespread depolarization may be connected with early microvascular alteration due to TBI because of the hereby induced massive generation of free radicals. There is evidence that due to ischemia and traumatic brain injury a Ca^{2+}-mediated impairment of vascular endothelia or vascular smooth muscles per se occurs, especially if the vessels are mechanically altered (BECKMAN et al. 1990). Therefore, an increase of endothelial $[Ca^{2+}]_i$ due to depolarization (see above) led to increased synthesis of NO, conversion of XDH to XO, and stimulation of phospholipase A_2; resulting in formation of platelet-activating factor (PAF) and free radicals (PATT et al. 1988). Microvessels might be the primary target of free radical damage because they contain a high concentration of xanthine dehydrogenase (XDH) / xanthine oxydase (XO), are exposed to high O_2 tensions, and are exposed to platelets and leukocytes. Conversion of XDH to XO is controlled by a limited Ca^{2+}-activated proteolysis; XO then can catalyze the oxidation of hypoxanthine or xanthine to uric acid with the simultaneous formation of O_2^- and H_2O_2. When these blood-formed elements attach to endothelial cells

they can initiate or enhance inflamatory reactions involving free radicals.

A possibly enhanced deterioration of the blood-brain barrier due to mechanical disturbance in the immature brain may be caused by its partly reduced antioxidative capacity. Ciriolo and co-worker have shown that the levels of antioxidant enzyme activities differ considerably in various brain parts (CIRIOLO et al. 1991). Furthermore, changes in the specific activities of superoxide dismutase, catalase, and glutathione peroxidase did not follow the same pattern as a function of aging. In particular, in the parietal cortex and the mesencephalon, superoxide dismutase and glutathione peroxidase activities increased, but the catalase activity decreased in the parietal cortex and did not change in the mesencephalon. In prefrontal cortex and caudate nucleus, superoxide dismutase and glutathione peroxidase activities did not change, while catalase activity decreased. The activity of glutathione peroxidase was increased in the hippocampus and was decreased in hypothalamus during aging (CIRIOLO et al. 1991). Therefore, an age-dependent regionally different susceptability to oxidative stress has to be considered.

Studies concerning the specific role of immature BBB function, i.e. its reduced expression of complex tight junction, in regard to the water and electrolyte balance after traumatic brain injury have not been done. We think that clarifying this could be considerably helpful for a better understanding of the mechanisms of water and electrolyte exchange between the vascular and brain extracellular compartment within the immature brain even in compromized conditions.

ICP increase – common consequences of diffuse brain swelling

Increased intracranial pressure is a common complication in infants and young children suffering from severe traumatic brain injuries, and closely correlates to adverse outcome. It was recently reported that about 60 % of severe head-injury patients develop an increased ICP, mostly as a result of brain swelling (WARD 1994). The incidence of brain swelling in pediatric patients was twice as high as in the adults (BRUCE et al. 1981; ALDRICH et al. 1992). This concurs with recent findings in experimental studies, where immature rats were discovered to develop cerebral edema more rapidly than mature rats (GRUNDL et al. 1994).

Which reasons may be responsible for this more frequent and obviously more easily induced response of increased ICP in the immature brain? According to the pressure-volume theory of determining intracranial compliance, an exponential portion of the pressure-volume curve results which is determined by the interrelationship between cerebrospinal fluid (CSF) formation, volume storage or compliance, and fluid absorption. The most pronouced peculiarity in the immature brain is the reduced intracranial compliance, which is up to 50 per cent worse in infants compared to adults when expressed as pressure-volume index. This compliance does not reach adult levels until fourteen years of age (SHAPIRO et al. 1980). Therefore, the immature brain must be much more susceptible to increase in ICP when a volume expansion of any cause happens. The steady-state equation describing ICP can be subdivided into two major components: CSF and vascular.

The CSF component consists of the formation resistance product and the vascular component of the dural sinus level. It was found that in head injured adults CSF parameters (including CSF resistance and absorption of fluid) accounted for appoximately 1/3 of the ICP rise and vascular mechanisms (i.e. increase in blood volume or indirectly by increasing tissue water) were the predominant factor in elevation of the ICP (MARMAROU 1996).

It has been proposed that the response to severe head injury in children differs from that in adults, with increased cerebral blood flow (cerebral hyperaemia) representing the most common cause of raised intracranial pressure. However, this has recently been disputed. Recent studies indicate that early response to severe TBI in young (ADELSON et al. 1997) and middle-aged children (SHARPLES et al. 1995) is accompanied by reduced CBF combined with a reduced cerebrovascular CO_2 reactivity (ADELSON et al. 1997) which leads to a poor outcome. Therefore, the rationale for therapeutical strategies to reduce TBI sequelae should focus on the improvement of cerebral metabolic conditions early after TBI. Mild hypothermia is now a well-established and highly effective means of cerebral protection.

Mild hypothermia

Mild hypothermia produces a marked protective effect on histopathological outcome after experimental brain trauma (DIETRICH et al. 1994), attenuating neurochemical sequels of cerebral oxygen lack and improving the behavioral outcome (CLIFTON et al. 1991). Possible explanations for hypothermia-related improvement include: (a) progressive reduction in cerebral metabolic rate of oxygen consumption, (b) alterations in ion homeostasis (including calcium and potassium fluxes), (c) increased membrane stability (including the blood-brain barrier), (d) altered enzyme function (e.g., phospholipase, xanthine oxidase, nitric oxide synthase activity), (e) alterations in neurotransmitter release and reuptake (e.g., glutamate), and (f) changes in free radical production or scavenging (for review see (DIETRICH 1996; WASS and LANIER 1996). Hypothermia has been evaluated as a therapeutic procedure for hastening neurological recovery and improving the outcome of adult patients with severe traumatic brain injury (MARION et al. 1997).

In a current study we examined the effects of mild hypothermia on cerebral hemodynamics and brain oxygen metabolism in two week old piglets following a step-

wise reduction in cerebral perfusion pressure, which was induced by gradual inflation of an epidural balloon. An experimental procedure was used which allows sequential estimation of regional CBF and $CMRO_2$. This was realized using an external closed-loop controller of arterial blood pressure in order to avoid ICP-related ABP alterations. We hypothesized that mild hypothermia may cause an improved cerebral oxygen balance during stages of decreased cerebral perfusion as a possible neuroprotective mechanism in juvenile brains.

We found that the presented results confirm the well-known effect of mild hypothermia on the decrease of cerebral oxidative metabolism. In piglets the reduction of metabolism occurs only as long as a widely unaltered cerebral O_2 delivery exists. However, if brain O_2 delivery was further reduced by CBF decrease induced by a gradual CPP reduction, then cerebral oxidative metabolism was easily determined by a more strongly reduced oxygen delivery to brain tissue. The previously existing $CMRO_2$ differences between normothermia and hypothermia ceased, although brain electrical activity was less suppressed in hypothermic animals (BAUER et al. 1998).

Conclusion remarks: specific features of the immature brain

There are distinct pecularities in the pathogenesis of brain edema formation within the immature brain. Further improvement of understanding the time course and the complex interactions in TBI edema formation needs new experimental approaches which take into account structural and functional features of brain development. This will deliver an improved basis for clinically motivated research in order to optimize the practice of infant and child TBI therapy.

References

ADELSON PD, CLYDE B, KOCHANEK PM, et al.: Cerebrovascular response in infants and young children following severe traumatic brain injury: a preliminary report. Pediatr Neurosurg 1997; **26** (4): 200–207.

ADELSON PD, KOCHANEK PM: Head injury in children. J Child Neurol 1998; **13** (1): 2–15.

ALDRICH EF, EISENBERG HM, SAYDJARI C, et al.: Diffuse brain swelling in severely head-injured children. A report from the NIH Traumatic Coma Data Bank. J Neurosurg 1992; **76** (3): 450–454.

ARMSTEAD WM, KURTH CD: Different cerebral hemodynamic responses following fluid percussion brain injury in the newborn and juvenile pig. J Neurotrauma 1994; **11**: 487–497.

ASTRUP J, SIESJÖ BK, SYMON L: Thresholds in cerebral ischemia. The ischemic penumbra. Stroke 1981; **8**: 723–725.

BAUER R, FRITZ H, WALTER B, et al.: Effect of moderate hypothermia on cerebral O_2 uptake during gradual cerebral perfusion pressure decrease in piglets. Pflügers Arch **435** Suppl. R 89.

BECKMAN JS, BECKMAN TW, CHEN J, et al.: Apparent hydroxyl radical production by peroxynitrite: implications for endothelial injury from nitric oxide and superoxide. Proc Natl Acad Sci U S A 1990; **87** (4): 1620–1624.

BRUCE DA, ALAVI A, BILANIUK L, et al.: Diffuse cerebral swelling following head injuries in children: the syndrom of "malignant brain edema". J Neurosurg 1981; **54**: 170–178.

CIRIOLO MR, FISKIN K, DE MARTINO A, et al.: Age-related changes in Cu,Zn superoxide dismutase, Se-dependent and -independent glutathione peroxidase and catalase activities in specific areas of rat brain. Mech Ageing Dev 1991; **61** (3): 287–297.

CLIFTON GL, JIANG JY, LYETH BG, et al.: Marked protection by moderate hypothermia after experimental traumatic brain injury. J Cereb Blood Flow Metab 1991; **11**: 114–121.

DIETRICH WD: Nonpharmacological strategies – moderate hypothermia. In: NARAYAN RK, WILBERGER JE, POVLISHOCK JT (eds.): Neurotrauma. McGraw-Hill, New York 1996, 1491–1506.

DIETRICH WD, ALONSO O, BUSTO R, et al.: Post-traumatic brain hypothermia reduces histopathological damage following concussive brain injury in the rat. Acta Neuropathol Berl 1994; **87** (3): 250–258.

DIJKHUIZEN RM, VAN LOOKEREN CAMPAGNE M, NIENDORF T, et al.: Status of the neonatal rat brain after NMDA-induced excitotoxic injury as measured by MRI, MRS and metabolic imaging. NMR Biomed 1996; **9** (2): 84–92.

DIXON CE, LIGHTHALL JW, ANDERSON TE: Physiologic, histopathologic, and cineradiographic characterization of a new fluid-percussion model of experimental brain injury in the rat. J Neurotrauma 1988; **5** (2): 91–104.

DOBBING J: The development of blood-brain barrier. Progr Brain Res 1968; **29**: 417.

D'SOUZA SW, MCCONNELL SE, SLATER P, et al.: N-methyl-D-aspartate binding sites in neonatal and adult brain [letter]. Lancet 1992; **339** (8803): 1240.

DUHAIME AC, CHRISTIAN C, MOSS E, et al.: Long-term outcome in infants with the shaking-impact syndrome. Pediatric Neurosurgery 1996; **24** (6): 292–298.

FADEN AI, DEMEDIUK P, PANTER SS, et al.: The role of excitatory amino acids and NMDA receptors in traumatic brain injury. Science 1989; **244** (4906): 798–800.

FODA MA, MARMAROU A: A new model of diffuse brain injury in rats. Part II: Morphological characterization. J Neurosurg 1994; **80** (2): 301–313.

GINSBERG MD: Injury mechanisms in the ischaemic penumbra: Approaches to neuroprotection in acute ischaemic stroke. Cerebrovasc Dis 1997; **7** Suppl.: 7–12.

GRUNDL PD, BIAGAS KV, KOCHANEK PM, et al.: Early cerebrovascular response to head injury in in immature and mature rats. J Neurotrauma 1994; **11**: 135–148.

HOSSMANN K-A: Periinfarct depolarizations. Cerebrovasc Brain Metab Rev 1996; **8**: 195–208.

ITO J, MARMAROU A, BARZO P, et al.: Characterization of edema by diffusion-weighted imaging in experimental traumatic brain injury. J Neurosurg 1996; **84**(1): 97–103.

JOHNSTON MV, SILVERSTEIN FS: Development of neurotransmitter. In: POLIN RA, FOX WW (eds.): Fetal and neonatal physiology (Second Edition). W.B. Saunders Company, Phiadelphia, 1998: 2110–2117.

KATAYAMA Y, MAEDA T, KOSHINAGA M, et al.: Role of excitatory amino acid-mediated ionic fluxes in traumatic brain injury. Brain Pathol 1995; **5** (4): 427–435.

LEVIN HS, ALDRICH EF, SAYDJARI C, et al.: Severe head injury in children: experience of the Traumatic Coma Data Bank. Neurosurgery 1992; **31** (3): 435–443.
LUERSSEN TG, KLAUBER MR, MARSHALL LF: Outcome from head injury related to patient's age. A longitudinal prospective study of adult and pediatric head injury. J Neurosurg 1988; **68** (3): 409–416.
MAIER HAUFF K, BAETHMANN AJ, LANGE M, et al.: The kallikrein-kinin system as mediator in vasogenic brain edema. Part 2: Studies on kinin formation in focal and perifocal brain tissue. J Neurosurg 1984; **61** (1): 97–106.
MARION DW, PENROD LE, KELSEY SF, et al.: Treatment of traumatic brain injury with moderate hypothermia. New Engl J Med 1997; **336**: 540–546.
MARMAROU A: Pathophysiology of intracranial pressure. In: NARAYAN RK, WILBERGER JE, POVLISHOCK JT (eds.): Neurotrauma. McGraw-Hill, New York 1996, 413–428.
MAYEVSKY A, DORON A, MANOR T, et al.: Cortical spreading depression recorded from the human brain using a multiparametric monitoring system. Brain Res 1996; **740** (1–2): 268–274.
MOSHE SL, ALBALA BJ, ACKERMANN RF, et al.: Increased seizure susceptibility of the immature brain. Brain Res 1983; **283** (1): 81–85.
NILSSON P, HILLERED L, OLSSON Y, et al.: Regional changes in interstitial K+ and Ca2+ levels following cortical compression contusion trauma in rats. J Cereb Blood Flow Metab 1993; **13** (2): 183–192.
OBRENOVITCH TP: The ischaemic penumbra: twenty years on. Cerebrovasc Brain Metab Rev 1995; **7** (4): 297–323.
ORR EL, PACE KR: The significance of mast cells as a source of histamine in the mouse brain. J Neurochem 1984; **42**: 727–732.
PALMER AM, MARION DW, BOTSCHELLER ML, et al.: Traumatic brain injury-induced excitotoxicity assessed in a controlled cortical impact model. J Neurochem 1993; **61** (6): 2015–2024.
PATT A, HARKEN AH, BURTON LK, et al.: Xanthine oxidase-derived hydrogen peroxide contributes to ischemia reperfusion-induced edema in gerbil brains. J Clin Invest 1988; **81** (5): 1556–1562.
ROGATSKY G, MAYEVSKY A, ZARCHIN N, et al.: Continuous multiparametric monitoring of brain activities following fluid-percussion injury in rats: preliminary results. J Basic Clin Physiol Pharmacol 1996; **7** (1): 23–43.
SCHILLING L, WAHL M: Brain edema: Pathogenesis and therapy. Kidney Intrnational 1997; 51, Suppl **59**: S69–S75.
SCHULZE C, FIRTH JA: Interendothelial junctions during blood-brain barrier development in the rat: morphological changes at the level of individual tight junctional contacts. Brain Res Dev Brain Res 1992; **69** (1): 85–95.
SHAPIRO K, MARMAROU A, SHULMAN K: Characterization of clinical CSF dynamics and neural axis compliance using the pressure-volume index: I. The normal pressure-volume index. Ann Neurol 1980; **7** (6): 508–514.
SHARPLES PM, STUART AG, MATTHEWS DS, et al.: Cerebral blood flow and metabolism in children with severe head injury. Part 1: Relation to age, Glasgow coma score, outcome, intracranial pressure, and time after injury. J Neurol Neurosurg Psychiatry 1995; **58** (2): 145–152.
SIESJÖ BK: Basic mechanisms of traumatic brain damage. Ann Emerg Med 1993; **22** (6): 959–969.
SIESJÖ BK, BENGTSSON F: Calcium fluxes, calcium antagonists, and calcium-related pathology in brain ischemia, hypoglycemia, and Spreading Depression: A Unifying Hypothesis. J Cereb Blood Flow Metab 1989; **9**: 127–140.
SLATER P, MCCONNELL SE, D'SOUZA SW, et al.: Postnatal changes in N-methyl-D-aspartate receptor binding and stimulation by glutamate and glycine of [3H]-MK-801 binding in human temporal cortex. Br J Pharmacol 1993; **108** (4): 1143–1149.
SPERBER EF, MOSHE SL: Age-related differences in seizure susceptibility to flurothyl. Brain Res 1988; **467** (2): 295–297.
STEWART P, HAYAKAWA E: Interendothelial junctional changes underlie the developmental "tightening" of the blood-brain barrier. Brain Res 1987; **429**: 271.
SYMON L, LASSEN NA, ASTRUP J, et al.: Thresholds of ischaemia in brain cortex. Adv Exp Med Biol 1977; **94**: 775–782.
TAVALIN SJ, ELLIS EF, SATIN LS: Mechanical perturbation of cultured cortical neurons reveals a stretch-induced delayed depolarization. J Neurophysiol 1995; **74** (6): 2767–2773.
TAVALIN SJ, ELLIS EF, SATIN LS: Inhibition of the electrogenic Na pump underlies delayed depolarization of cortical neurons after mechanical injury or glutamate. J Neurophysiol 1997; **77** (2): 632–638.
UNTERBERG A, WAHL M, HAMMERSEN F, et al.: Permeability and vasomotor response of cerebral vessels during exposure of arachidonic acid. Acta Neuropathol 1984; **73**: 209–219.
VAN DEN BRINK WA, SANTOS BO, MARMAROU A, et al.: Quantitative analysis of blood-brain barrier damage in two models of experimental head injury in the rat. Acta Neurochir Suppl Wien 1994; **60**: 456–458.
VERHEUL HB, BALAZS R, BERKELBACH VAN DER SPRENKEL JW, et al.: Temporal evolution of NMDA-induced excitoxicity in the neonatal rat brain measured with 1H nuclear magnetic resonance imaging. Brain Res 1993; **618** (2): 203–212.
WALTER B, BAUER R, ZWIENER U: Stimulation of the median nerve increases intracranial pressure after severe neonatal asphyxia. Pflügers Arch. 1998; **435** Suppl: R 238.
Walter B, BAUER R, FRITZ H, et al.: Use of micro tip pressure transducers for measurement of intracerebral pressure transients induced by fluid percussion. Exp Toxic Pathol 1999; **51**: 124–129.
WARD JD: Pediatric head injury: A further experience. Pediatr Neurosurg 1994; **20**: 183–185.
WASS CT, LANIER WL: Hypothermia-associated protection from ischemic brain injury: implications for patient management. Int Anesthesiol Clin 1996; **34** (4): 95–111.
ZAUNER A, BULLOCK R, KUTA AJ, et al.: Glutamate release and cerebral blood flow after severe human head injury. Acta Neurochir Suppl Wien 1996; **67**: 40–44.