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Pathophysiology of traumatic injury in the developing brain: an introduction and short update ☆

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Abstract

Current understanding about the main peculiarities in pathophysiology of immature brain traumatic injury involves marked developmental discrepancy of biomechanical properties, aspects of altered features in water and electrolyte homeostasis as well as maturation dependent differences in structural and functional responses of major transmitter systems.

Based on the fact that traumatic brain injury (TBI) is one of the major causes of morbidity and mortality in infants and children, the currently available epidemiological data are reviewed in order to gain insights about scope and dimension of health care engagement and derive the requirements for reinforced pathogenetic research.

To this end, the main aspects of peculiarities in primary and secondary TBI mechanisms in the immature/developing brain are discussed, including structural and functional conditions resulting in a markedly diminished shear resistance of the immature brain tissue. As such, the immature brain tissue appears to be more susceptible to mechanical alterations, because similar mechanical load induces a more intense brain tissue displacement. Furthermore, available indications for increased incidence of brain swelling in the immature brain after TBI are reviewed, focusing on the interrelationship between the age-dependent differences in extracellular space and aquaporin-4 expression during brain maturation. The developmental differences of TBI induced cerebrovascular response as well as some relevant aspects of altered neurotransmission following TBI of the immature brain in regard to the glutamatergic and dopaminergic transmitter system are assessed.

Thus, this mini-review highlights some progress but also an increased necessity for expanded pathogenetic research on a clinical scale in order to develop a solid foundation for adequate therapeutic strategies for the different life-threatening consequences of TBI in infancy and childhood, which mainly have failed up to now.

Keywords: Pediatric TBI; Pathogenetic models; Review

Introduction

Head trauma or traumatic brain injury (TBI) in infancy and childhood is still the single most common cause of death (Graham, 2001; Luerssen et al., 1988) and permanent disability. Despite an increased body of

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evidence that pediatric TBI exhibits a uniqueness compared with head injuries in adults, there is still a serious deficit in clarification of the specific pathogenesis of pediatric TBI. Therefore, accepted treatments used in pediatric TBI are still based on adult therapeutic principles, which do not consider adequately effects of age, level of brain maturation and other structural and functional developments (Adelson and Goldstein, 2002). Nevertheless, relevant progress in understanding of several relevant aspects of the complex dynamics in pediatric TBI pathogenesis has been made to verify some specificity of trauma-related response of the immature brain (Adelson and Kochanek, 1998; Kochanek et al., 2001). A short introduction will be given highlighting current insights into certain aspects in pathophysiology of pediatric TBI in a general manner in order to promote and facilitate gradation and assessment of special issues, like biomechanics of the immature brain, role of apoptosis as well as dopaminergic response and recent promising strategies for effective pediatric TBI treatment including the optimal management of posttraumatic hypothermia.

Relevance of TBI in infancy: epidemiological findings

TBI accounts for over 50% of deaths in the pediatric population with two peak periods of incidence. The first peak occurs in children < 4–5 years old, and the second is in mid to late adolescence (Levi et al., 1991; Ward, 1996; Wegman, 1982). The incidence of TBI in different countries appears to vary greatly: whereas in the USA an annual incidence rate between 185 and 300 per 100,000 children remains at a markedly high level (Adelson and Kochanek, 1998), despite increasing endeavors for prevention, appears the epidemiological situation in smaller European countries markedly better. Recent Swedish data reported a mean incidence rate of 12 cases of pediatric TBI per 100,000 (Emanuelson and v Wendt, 1997), presumably resulting from more favorable socioeconomic conditions, but the underlying causal relations remain unknown. For most communities, exact epidemiologic data about frequency, type and severity of pediatric TBI are lacking.

Available findings suggest a similar distribution in severity of head injuries in different age groups. Classification is mostly done using the Glasgow Coma Scale (GCS) (Teasdale and Jennett, 1974, 1976), which has gained broad acceptance for the assessment of the severity of brain damage (Feickert et al., 1999; Sternbach, 2000), although applying this scale to infants and younger children can be problematic, particularly in the ''verbal/face'' component (Durham et al., 2000). Whereas studies suggest that the pediatric age group more often shows some milder injuries than the adults (86% vs. 79%) (Luerssen et al., 1988), it has become increasingly recognized that these children also can suffer significant cognitive deficits that can permanently impact on concentration, complex thinking, decision-making capability, and of particular importance of complex psychosocial interaction (Anderson et al., 2001) as well as novel psychiatric disorders like attention deficit/hyperactivity disorder and depressive disorder (Bloom et al., 2001). Furthermore, there is evidence that age has a strong influence on incidence (as mentioned above) and outcome. Comparison of age-defined subgroups of patients revealed that outcome was poorest in the 0- to 4-year-old patients, as reflected by their mortality. In contrast, school-age children showed an improved survival rate, twice that known from adult data, whereas adolescents exhibited a similar outcome to adults (Levin et al., 1992). However, a current retrospective study about the impact of risk factors on outcome in severely head injured children, representative of a large metropolitan plus rural area in the middle of Europe, revealed that age has no significant influence on mortality (Feickert et al., 1999). In addition, in this study a reduced overall mortality rate (22%) of children with severe head injury was documented, similar to previous findings (Ward, 1994). This indicates a somewhat promising tendency because older studies consistently reported markedly higher death rates of between 25% and 45% (Berger et al., 1985; Eichelberger et al., 1988; Haller, 1983; Kraus et al., 1987; Luerssen et al., 1988). Nevertheless, although children have better survival rates compared with adults with TBI, the long-term sequeals and consequences are often more devastating in children due to their age and developmental potential (Feickert et al., 1999; Mazzola and Adelson, 2002; Pfenninger and Santi, 2002).

Peculiarities in primary and secondary mechanisms of traumatic injury in the immature/developing brain

Pediatric head injuries vary widely in their etiology, pathophysiology, clinical presentation, and optimal treatment strategies. Resulting brain injury, characterized by structural failure and neurological dysfunction, is a result of direct and indirect damage that begins at the time of injury and lasts from hours to weeks after the initial insult. In principle, two categories of brain injury can be differentiated into focal injuries and diffuse injuries. Focal brain injuries, which are usually caused by direct force effects to the head, comprise contusions, brain lacerations, and hemorrhage leading to the formation of hematoma in the extradural, subarachnoid, subdural, or intracerebral compartments within

the head (Adelson and Kochanek, 1998). Diffuse brain injuries, which are usually caused by a sudden movement of the head, comprise classical brief cerebral concussion and more prolonged posttraumatic coma, also known as diffuse axonal injury. Mechanistically considered, primary traumatic effects involve neural or vascular elements of the brain, which can be affected by delayed effects such as deafferentation or secondary events such as ischemia, swelling, cerebral edema, and increased intracranial pressure (ICP) (Gennarelli, 1993).

The progressive nature of pediatric brain injury is a combination of mechanical forces and pathophysiological events. As a result of initial mechanical forces, a cascade of neural and vascular events with age-related properties occur, which determines the clinical syndrome of TBI and its consequences.

Key features of biomechanics in infancy

There are unique responses to TBI in the pediatric population compared to similarly injured adults, which are primarily based on structural differences. The main structural differences consist in an increase in water content of the brain tissue (see Fig. 1), capillary density (Feher et al., 1996) and cerebral blood volume (Bauer et al., 1999), and a reduced extent in myelination (Dobbing, 1981), which result in a markedly diminished shear resistance (Thibault and Margulies, 1998). Therefore, the immature brain tissue appears to be more susceptible to mechanical alterations, because similar mechanical load induces a more intense brain tissue displacement. Hence, a more intense intracerebral shear stress results. In addition, brain protection by the surrounding structures, especially the skull, is markedly reduced because of the immature skull bone sutures and insufficient calcification. Thus, a significant increase in skull elasticity results. Consequently, mechanical load is more easily transferred to the brain tissue through the comparatively compliant skull and membranous suture properties of the infant brain case (Walter et al., 2001). This is associated with large cranial shape changes, and a more diffuse pattern of brain distortion compared with adult properties (Margulies and Thibault, 2000). Therefore, primary sequels of head trauma in infants exhibit unique patterns due to age-related biomechanical properties.

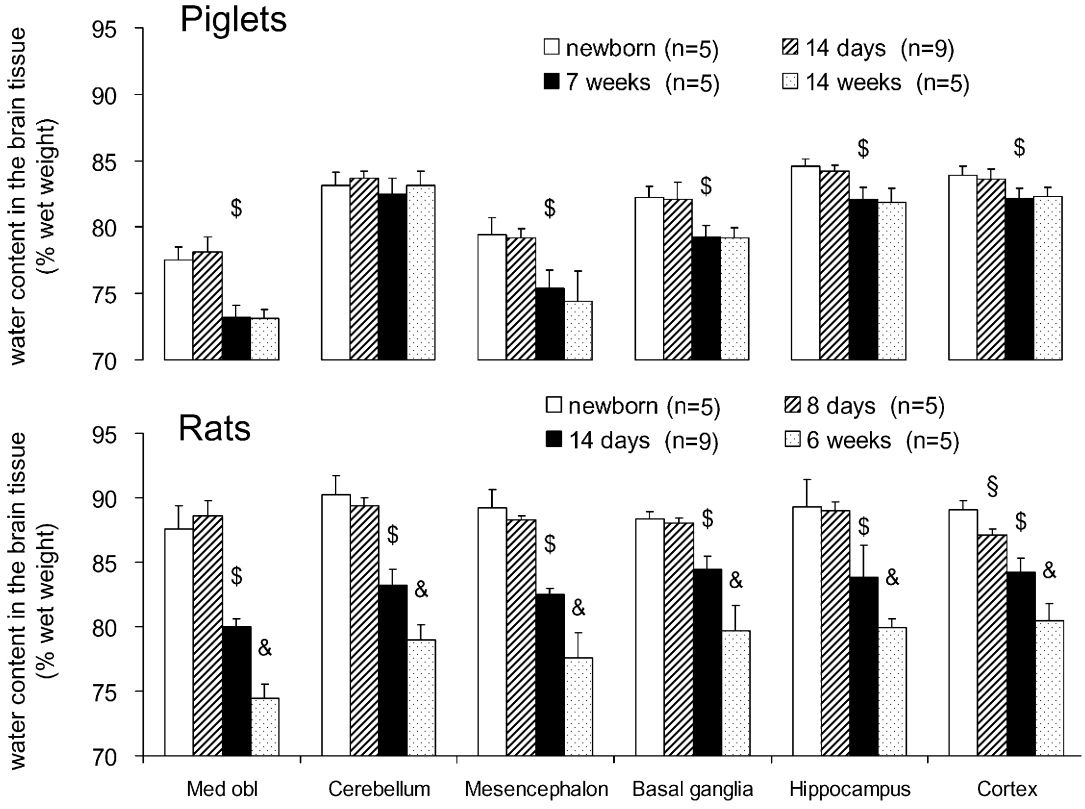

Fig. 1. Age dependency of regional brain water content in piglets and rats, estimated by wet weight/dry weight measurements. Note the marked interspecies differences in absolute amounts of the water content during the early postnatal period, whereas the water content at the juvenile age appears quite similar in these peri- vs. postnatal brain developers (Dobbing, 1981). (Values are presented as means + SD, § $ & $p < 0.05$, one-way ANOVA, § $ & indicate significant differences of adjacent age groups).

Brain swelling: what are the indications for increased incidence in the immature brain after TBI

Diffuse brain swelling (DBS) after severe TBI occurs more commonly in children than adults (Adelson and Kochanek, 1998; Aldrich et al., 1992; Bruce et al., 1981). Furthermore, children found to have DBS have a threefold higher mortality rate than those without it (Aldrich et al., 1992). 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 have been rare. However, pathogenetic mechanisms of edema formation after TBI in the immature brain appeared to be different in comparison to adult brains. There is evidence that vasogenic as well as cytotoxic edema components (Klatzo, 1967) may be responsible for the development of DBS. Besides mechanical disturbance, the blood–brain barrier (BBB) 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 (Adelson et al., 1997). Moreover, a transient increase of glutamate receptor expression at this period of life may be responsible for an increased threat of intracellular sodium ion accumulation in brain cells (see below). In contrast to many other organs, the increase of brain water content is a serious condition which becomes life threatening if ICP increases because of volume expansion at largely restricted intracranial space (Monro-Kellie Doctrine: An increase in the volume of any one of the components of the brain requires a corresponding decrease in the volume of the other two components), thereby reducing cerebral perfusion pressure (CPP) and, hence, cerebral blood flow. Impaired CBF appears to be the most frequent cause for secondary brain injury after TBI.

What are the basic properties which may be responsible for disturbed water movements in the immature brain owing to mechanical injury? First of all, water content in the brain tissue is age-dependent, but time course of reduction is species-dependent (Fig. 1). This property corresponds with an enlarged extracellular space volume (ECS) of immature brain tissue. Until now, related data have only been available from rats. As shown by Lehmenkuhler et al. (1993) newborn rat exhibits an ECS in gray and white matter, which is more than twice as large as known in the adult rat brain. The earliest decrease in volume fraction was found in layers V and VI at postnatal days 6–7 followed by a decrease in layer III and IV at postnatal days 8–9 and in white matter at postnatal days 10–11. A further dramatic reduction in volume fraction occurred in all cortical layers and especially in the white matter between postnatal days 10 and 21. There was no further decrease in volume fraction between postnatal day 21 and adults (Lehmenkuhler et al., 1993). However, further diffusion characteristics (tortuosity, nonspecific cellular uptake of tetramethylammonium) did not show any age-dependent alterations. The dramatic ECS reduction corresponds with an extensive growth and migration of neuronal elements. The total thickness of the gray matter is almost doubled in the first 15 days. Furthermore an extensive gliogenesis occurs during the same developing period in gray matter. The delayed white matter ECS reduction is obviously linked with onset of the period of extensive myelinization. Therefore, it is clear that species-specific differences of diffusion properties correspond with varying dynamics of the structural development.

Secondly, water can pass directly through the normal lipid bilayer of the plasma membrane, but this form of water flux is slow and not subject to regulation. In contrast, it has long been recognized that water permeability in the brain is remarkably high: approximately 50% of all brain water is exchanged by bidirectional diffusion within seconds (Behring, 1952). Given that water molecules are moved passively, driven by chemical gradients, regulation of water movement and its disturbance must be realized at the blood–brain exchange surface. Recently, it has been shown that specialized water channels (aquaporin 4 (AQP4)) are extensively expressed in the brain and appear to be crucial to the physiological and pathophysiological handling of water (for Review see (Amiry-Moghaddam and Ottersen, 2003). The water channel protein AQP4 is strongly expressed in astrocytes but not in neurons, which point to the central role of glia in brain water homeostasis (Jung et al., 1994; Nielsen et al., 1997). Moreover, the subcellular distribution of AQP4, enriched expression in the glial end feet, suggests a pivotal role for exchange of water with blood and cerebrospinal fluid (CSF) (Nielsen et al., 1997). Pericapillary astrocyte end-feet are the first cellular elements to swell during brain ischemia (Dodson et al., 1977). Astrocyte swelling can result from uptake of extracellular K^+, Cl^-, and Na^+ with subsequent osmotic movement of water (Kimelberg, 1995). Recently, a volume-sensitive organic osmolyte/anion channel has been identified in human glial cells (Jackson and Madsen, 1997). It mediates organic osmolyte efflux in response to cellular swelling. It may be hypothesized that the astrocytes respond to extracellular environmental changes during tissue injury by taking up various osmoles to provide a more ideal environment for neurons to survive.

Maturation of glial AQP4 expression spans a rather long period of time: as shown in the rat brain only 2% of the adult level was found at postnatal day 7 with a pronounced appearance at day 14 with 25%, whereas

about 60% was found at day 28 (Wen et al., 1999). In contrast, in avian (chick) brain with a precocious cerebral electric activity and cerebral capillary proliferation, the expression of AQP4 water channels occur during early embryonic development in ependymoglial cells and astroglia (Nico et al., 2001). There is evidence that AQP4 is coupled functionally and spatially to proteins that are responsible for K^+ buffering. So it is likely that AQP4 primarily serves to mediate activity-dependent water fluxes that are required to sustain ion and volume homeostasis at central synapses. Therefore, ontogeny of brain water flux regulation appears to be associated with functional development.

In regard to water accumulation in the brain, i.e. brain edema, perivascular AQP4 might have a specific role: water flux through AQP4 is bidirectional and driven solely by osmotic gradients (Nielsen et al., 1997). It has been shown that knocking out AQP4 reduced the extent of edema after experimental stroke or hypo-osmolar stress by about 50% (Manley et al., 2000). Furthermore, it has been shown that AQP4 is lost from perivascular membranes in the post-ischemic period, which may retard the dissipation of postischemic brain edema (Amiry-Moghaddam et al., 2003). This selective lost of perivascular AQP4 apparently results from its specific anchoring on the cytoskeleton by α-syntrophin, which in the astroglial endfeet is connected to the extracellular matrix by the dystrophin-associated protein complex. Transient cerebral ischemia led to a disturbance of α-syntrophin-dependent anchoring of AQP4. A similar reduction of brain AQP4 has been reported after focal TBI in adult rats (Kiening et al., 2002). Focal TBI in the adult rat brain led to an upregulation of AQP4 at the site of TBI and a down-regulation of this molecule adjacent to the site of injury (Sun et al., 2003). However, the significance of age-dependent expression of glial AQP4 for disturbed brain water balance after TBI in the immature brain has to be resolved. Even if no data exist about the pathophysiological role of aquaporins at the dystrophin-associated protein complex in the immature brain thus far, the delayed expression of AQP4 during ontogeny suggests an involvement in compromised capacity of accumulated water resolving. An improved understanding of the physiology of AQP4 and its regulation following brain injury may allow for the development of novel treatments for cerebral edema that accompanies head injury.

Thirdly, maturation of the BBB involves essentially the protection of brain tissue against influx of hydrophilic small molecules, like ions or amino acids and plasma proteins. The capillary endothelial cells of the vertebrate brain express epithelial-like high resistance tight junctions that fuse the plasma membranes of neighboring capillary endothelial cells in the brain (Reese and Karnovsky, 1967). Structural maturation is largely finished during intrauterine development, characterized in rat by the increase in the ratio of ''narrow zones'' to ''wide zones'' in the interendothelial clefts (Schulze and Firth, 1992) and the rapid increase in the transendothelial electrical resistance of pial vessels (Butt et al., 1990). Hence, early in development BBB is effective in restricting entry of proteins from blood into the intercellular environment of brain tissue (Saunders et al., 2000). However, the protein content of the CSF shows an age-dependent and brain maturation-dependent profile with highest values early in fetal life and then gradual decline (Dziegielewska et al., 2000). Interestingly, already in early stages of brain development, the highly concentrated proteins in CSF are excluded from the extracellular fluid by the presence of barriers at the CSF–brain interfaces, which disappear during maturation. Indeed, a transcellular mechanism has been characterized, which specifically transfers some plasma proteins across choroids plexus epithelial cells (Knott et al., 1997). Thus, the altered CSF composition during development is clearly a sign of developmental specificity of brain maturation rather than an indicator for blood–CSF barrier immaturity.

To summarize, despite marked developmental peculiarities of water homeostasis, until now there is no sufficient concept to clarify specific mechanisms responsible for the pronounced risk of DBS in the immature brain. Nevertheless, the development of brain edema can no longer be reduced to an issue of osmotic forces acting across a lipid bilayer. The unraveling of a molecular basis for brain edema formation may offer new possibilities for treatment of this potentially lethal condition (Amiry-Moghaddam and Ottersen, 2003). However, the current treatment strategies in infants and children suffering TBI mostly target cerebral swelling more or less non-specifically by osmotherapy, decompressive craniectomy, hypothermia, and controlled hyperventilation (Bayir et al., 2003).

Vascular response in immature brain after TBI: Hyperemia versus ischemia; age-related effects of cerebrovascular regulation

Hyperemia, a cerebral blood flow in excess of brain tissue demand, has long been considered to be a main cause of raised ICP after TBI, particularly in the immature brain. However, experimental and clinical studies have reported inconsistent findings. An early clinical study showed that in young adults a coincidence between high CBF and brain swelling existed with a decrease after resolution of swelling, whereas patients without signs of DBS showed lower CBF values (Bruce et al., 1981). The authors argued that hyperemia was the cause of brain swelling in accordance with the Monroe-Kellie doctrine. Experimental evidence was delivered recently that posttraumatic hyperemia appears to be an

age-dependent phenomenon. A marked regional CBF increase was found 24 hours after local TBI in immature and mature rats, but not in aged animals. However, global increases in CBF were not observed (Biagas et al., 1996). In contrast, in the largest report of CBF after severe TBI in infants and young children, hypoperfusion was common during the first 24 hours, and ischemia (global CBF < 20 mL/100 g/min) was associated with poor outcome (Adelson et al., 1997). Age-dependent hemodynamic effects of TBI have been studied extensively in the piglet model using fluid percussion injury (for review see (Armstead, 2000). Major findings were a long-lasting pial artery vasoconstriction and reduced CBF in newborns, whereas similar alterations are smaller in magnitude and duration in juvenile animals (Armstead, 1999; Armstead and Kurth, 1994). In contrast, a comparison between juvenile and adult rats showed a blunted amount of CBF reduction after weight drop induced TBI of the younger animals, despite a more pronounced water accumulation (Grundl et al., 1994). Importantly, hypotensive cerebral autoregulation is impaired to a greater degree and for a longer time after moderate FP-TBI in the newborn compared to juvenile pigs (Armstead, 1999). As outlined in detail in a parallel contribution (Armstead, this volume), a mechanistic explanation involves impaired NMDA receptor mediated vasodilation after TBI which is more compromised in the injured immature brain.

Developing aspects of altered neurotransmission following TBI: glutamatergic/dopaminergic activity; oxidative stress

Excitotoxicity reveals deleterious consequences of supraphysiologic levels of glutamate and other excitatory amino acids. In brief, activation of NMDA receptors and metabotropic glutamate receptors contribute to intracellular Ca^{2+} overload. As a result of glutamate mediated overactivation, Na^+ and Cl^- enter the neurons via AMPA receptor channel. Water follows passively, as the influx of Na^+ and Cl^- is much larger than the efflux of K^+ (cytotoxic brain edema). There are, however, age-dependent differences in the susceptibility of glutamate receptors to excitotoxicity in the developing brain. NMDA receptor activation in the immature brain induces an increased calcium influx than in the adult brain (Burnashev et al., 1992), suggesting an increased burden on the immature brain from excitotoxic brain injury. However, the temporary NMDA receptor overexpression appears also to be a period of increased vulnerability in regard to pivotal necessity of adequate excitatory input, primarily via NMDA receptors. A short-term blockade of NMDA receptors induces a markedly aggravated apoptotic neurodegeneration in the developing brain (Ikonomidou et al., 1999). A thorough review of the interrelation between TBI induced apoptotic neurodegeneration and the role of excitotoxicity is given by Bittigau et al. (this volume).

However, the role of the dopaminergic system in the pathogeneses of TBI has received less attention, despite the fact that growing evidence exists that altered dopaminergic activity is involved in long-term sequels after TBI. Beside other symptoms of frontal lobe syndrome TBI often produces devastating attentional disorders (Whyte et al., 1996). In addition, several well-controlled studies about the efficacy of dopamine uptake blockers support findings in rats of improved recovery of spatial acquisition deficits after TBI (Kline et al., 2000) and suggest that these drugs predominantly affect the speed of cognitive processing and certain observational ratings of mood and behavior during rehabilitation of patients suffering TBI (Whyte et al., 2002). However, in regard to underlying mechanisms controversial results have been reported. An improvement of working memory and spatial acquisition deficits after chronic bromocriptine treatment of rats and humans after TBI suggests the involvement of dopamine 2 (D_2) receptor activation (Kline et al., 2002; McDowell et al., 1998). In contrast, an improvement of memory dysfunction associated with TBI in mice was brought about by D_2 receptor antagonist administration (Tang et al., 1997). However, the age-dependency of dopaminergic sensitivity to TBI has seldom been studied. Some indications came from similarities in motivational disturbances reported in children suffering from TBI and attention deficit/hyperactivity disorder (ADHD). Both groups showed comparable deficits in impulse control. It was concluded that slowing of information processing speed seems to be a general consequence of TBI in childhood (Konrad et al., 2000). ADHD is obviously associated with abnormalities in the dopaminergic system (Dougherty et al., 1999; Ernst et al., 1999; Krause et al., 2000; Vles et al., 2003). In a current report it has been shown that severe FP-TBI induces an upregulation of dopaminergic activity in the mesotelencephalic dopaminergic system of newborn piglets which is not related to alterations in brain oxidative metabolism (Walter et al., 2004). In contrast, the juvenile pigs did not show any comparable TBI-induced alterations in the brain dopaminergic system.

The biological significance of an increased dopaminergic activity is based on the hypothesis that this is related to an increase in extracellular dopamine $[DA]_e$ early after FP-TBI in newborn piglets. It is suggested that an increase of $[DA]_e$ plays an important role in the pathogenesis of neuronal injury in the newborn brain. This is supported by numerous findings from different injury models. Direct neurotoxic effects of DA on cultures have been shown (Rosenberg, 1988). Furthermore, DA obviously plays an important

role in ischemia-reperfusion injury, because it has been suggested that an increase in extracellular dopamine can result in alterations in the sensitivity of neurons to excitatory amino acids (Globus et al., 1988).

Another proposed mechanism for the neurotoxic effect of DA is through an increase of the production of free radicals. There are several pathways for free radical generation in the brain, to which dopamine may contribute. Oxidation of the excess dopamine released during ischemia by molecular oxygen may occur during reperfusion. Dopamine can react with hydroxyl radicals to form the dopaminergic neurotoxin, 6-hydroxydopamine, which generates free radicals during its spontaneous rapid autooxidation (Slivka and Cohen, 1985). Furthermore, the enzymatic oxidation of DA by monoamine oxidase results also in the formation of hydrogen peroxide, a hydroxyl radical precursor (Maker et al., 1981).

In conclusion, this main final pathway of free radicals production and its role in irreversible deterioration of brain tissue should be discussed, for it is also thought to be a principal pathogenetic gate during excitotoxicity induced by TBI and its secondary sequels, like ischemia and inflammation (Feuerstein et al., 1997; Johnston et al., 2001; Tyurin et al., 2000). The indications for a progressive compromise of antioxidant defenses and evidence of free radical-mediated lipid peroxidation have been reported in pediatric TBI (Bayir et al., 2002). Furthermore, free radicals can be responsible for protein and DNA oxidation, and activation of transcription factors, causing dysregulation of cellular homeostasis after TBI. The immature brain appears to be selectively vulnerable to oxidative stress. The enhanced neurotoxicity from hydrogen peroxide accumulation is associated with inadequate scavenging abilities of the immature nervous system, such as lower glutathione peroxidase activity (Fullerton et al., 1998). Contributing to the immaturity of the scavenging enzymes is the inability of the developing nervous system to maintain glutathione stores. The immature nervous system is rich in iron, and has more free iron than the mature nervous system. As hydrogen peroxide accumulates because of these inappropriate defense mechanisms, it is exposed to this free iron. This exposure results in the generation of OH radical (Fenton reaction), a more potent free radical that can cause severe damage. The rapid conversion of hydrogen peroxide to OH radicals in the setting of free iron sets up the immature nervous system for increased cytotoxicity (Blomgren et al., 2003; Ferriero, 2001).

Understanding the molecular mechanisms of water homeostasis, excitotoxicity, apoptosis and oxidative stress will lead to better therapies for traumatic injury of the immature brain.

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