Lung Disease and Brain Development

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Lung Disease and Brain Development

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Key Words

Prematurity · Developmental plasticity · Glucocorticoids · Magnetic resonance imaging

Abstract

With the technical progress made in fetal and neonatal intensive care, perinatal mortality has decreased by 25% over the last decade and has expanded the surviving premature population. Prematurity drastically changes the environment of the developing organism. Striking evidence from a number of disciplines has focused attention on the interplay between the developing organism and the circumstances in which it finds itself. The environmental event during a sensitive period in development, induces injury and/or biological adaptations that lead to altered differentiation of tissues. The organism can express specific adaptive responses to its environment which include short-term changes in physiology as well as long-term adjustments. This review addresses these short-term as well as longer-term changes occurring in lung and brain tissue and illustrates how these changes can be studied using advanced imaging techniques such as magnetic resonance imaging (MRI).

Abbreviations

ADC	apparent diffusion coefficient	IFN-γ	interferon
AP-1	activating protein 1	IGF-1	insulin-like growth factor
Bax	pro-apoptotic protein	IL-6, 9, 1β	interleukins
Bcl-2	anti-apoptotic protein	MR	mineralocorticoid receptor
BDNF	brain-derived neurotrophic factor	MRI	magnetic resonance imaging
bFGF	fibroblast growth factor	MMP	metalloproteinases
BPD	bronchopulmonary dysplasia	NF-kappa B	nuclear factor kappa B
c-fos	activated transcription factor	NMDA	N-methyl-*D*-aspartate receptor
CSF	cerebrospinal fluid	NO	nitrogen oxide
3D-MRI	three-dimensional quantitative magnetic resonance imaging	NT-3	neurotrophin
		PAF	platelet activating factor
DEX	dexamethasone	PDGF	platelet-derived growth factor
DTI	diffusion-tensor imaging	TGF-β	transepidermal growth factor
DWI	diffusion-weighted imaging	TIMP	tissue inhibitors of metalloproteinase
GC	glucocorticoid	TNF	tumor necrosis factor
GR	glucocorticoid receptor	VEGF	vascular endothelial growth factor

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Long-term survival for premature infants (<32 weeks) has become an almost expected outcome over the past two decades. Progressive improvements in neonatal care have expanded the premature population so that it now comprises approximately 2.5% of total annual births. With this improvement in survival rate, the focus has shifted to the immediate and later consequences of prematurity. Adverse outcome is linked to factors related to antenatal insults such as maternal-fetal infection, perinatal illness such as lung disease or focal brain lesions and general factors such a sex, ethnic group and social class [1–3].

Striking evidence from a number of disciplines has focused attention on the interplay between the developing organism and the circumstances in which it finds itself [4]. The organism can express specific adaptive responses to its environment which include short term changes in physiology as well as long-term adjustments. The concept of 'developmental plasticity or disruption of the developmental program' summarizes the events of such adjustment. The environmental event during a sensitive period in development, induces injury and/or biological adaptations that lead to altered differentiation of tissues and organs, with consequent function that may diverge from normal [5–7]. Prematurity, could be one of these conditions where disruption of the developmental program or developmental plasticity in lung and brain will have a major effect on long-term outcome [7] (fig. 1).

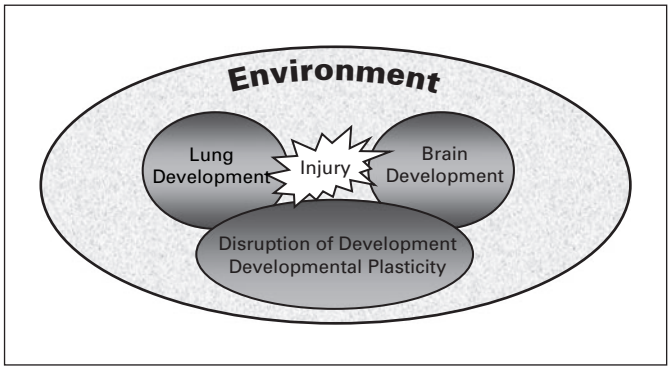

Fig. 1. General concept of modulation of organ development by environmental cues involving disruption of developmental program and developmental plasticity.

Developmental Plasticity in the Brain

The developing brain is one of the organs particularly prone to be affected by endogenous and exogenous events through the fetal and early postnatal life [8]. Mechanisms known to provide plasticity include deletion of neurons through apoptosis, proliferation and pruning of synapses, activity-dependent modeling of synaptic connections and for certain areas persistence of neuronogenesis. During normal development between 15 and 50%, according to brain areas, of the initially formed neurons will be eliminated by a physiological process called programmed cell death or apoptosis. About 70% of these neurons that are destined to disappear seem to die between 28 and 41 gestational weeks [9].

This programmed cell death is a complex mechanism which involves a balance between death and trophic signals, death and survival genetic programs, and effectors and inhibitors of cell death modified by environmental cues [10]. In this process, activation of the cascade of caspases (proteolytic enzymes) is a key step leading to DNA fragmentation and neuronal cell death. Caspase pathway can be activated by a mitochondrial-dependent pathway controlled by members of the Bcl-2 family or by activation of death receptors, a subgroup of the TNF receptor superfamily [11]. Exposure to challenging experiences may further alter developing glial cells. The glial progenitors originate from the proliferative subventricular zone. They are produced during the last months of gestation and in the early postnatal period. During migration within the white matter, differentiation occurs, e.g., into the preoligodendrocytes. Growth factors, hormones and cytokines (bFGF, NT-3, PDGF, IGF-1, IL-6, thyroid hormone) are implicated in oligodendrocyte maturation but up to 50% of oligodendrocytes undergo programmed cell death (apoptosis) during development with similar interactions with environmental cues [12]. Such glial plasticity may parallel neuronal remodeling [13]. During brain development, there are successive waves of overproduction of labile synapses, inducing redundant connections. This step is under tight genetic control. Each wave of overproduction is followed by a period of stabilization of synapses. This period of stabilization and elimination is highly influenced by environmental stimuli and experience [14]. Neuronal activity-mediated glutamate release will induce at the level of NMDA receptors a post-synaptic calcium influx. Calcium changes will lead to production of trophic factors such as brain-derived neurotrophic factor (BDNF), which will stabilize labile synapses, protecting them against elimination. NO which is rapidly produced after glutamate binding to its NMDA receptor is another key player in synaptic stabilization and plasticity. Successive waves of synaptogenesis have been

described with a most productive phase between midgestation and around 8 months postterm [15].

Altering gene expression is another way of tissue programming. Signaling pathways modulating NF-kappa B activity [16, 17] include those engaged by neurotrophic factors, neurotransmitters, electrical activity, cytokines, and oxidative stress. NF-kappa B activation can prevent the death of neurons by inducing the production of antiapoptotic proteins such as Bcl-2. Inhibition of NF-kappa B results in reduced size and complexity of neurite and dendritic arbors of somatosensory neurons [18]. These findings support a pivotal role for NF-kappa B as a mediator of transcription-dependent enduring changes in the structure and function of neuronal circuits [19, 20]. Increase in white matter connectivity and volume, growing complexity of neuronal networks suggested by gray matter changes, and environmentally sensitive plasticity are all essential aspects in a child's ability to mentalize and maintain the adaptive flexibility necessary for healthy transition into adulthood [21]. In a time where methodological advancement in neuroimaging has opened up new ways for examining the developing human brain in vivo, the study of structural developmental plasticity has become possible. Neuroimaging is providing new insights into the dynamics of neural circuits involved in cognitive and behavioral development and molecular genetic research is producing and abundance of new target molecules for the identification of developmental disorders as well as potential neuroprotective agents [22, 23].

Understanding the effects of antenatal, perinatal and neonatal events on later structural and functional brain development – aberrant or regenerative – will be essential for the development of treatments in obstetrics and neonatology to prevent developmental disabilities having their origin in early life.

Developmental Plasticity in the Lung

Neonatal lung disease occurs during ongoing lung development. A complex set of morphoregulatory molecules that fall into three classes: transcription factors [e.g. Nkx2.1, GATA, hepatocyte nuclear factor (HNF)-3]; signaling molecules [FGF, bone morphogenetic protein (BMP)-4, platelet-derived growth factor (PDGF), *Sonic hedgehog* (*Shh*), TGF-β]; and extracellular matrix proteins and their receptors (collagen, laminin, integrins, cadherins) control lung development. Proximal lung morphogenesis is independent of Nkx2.1 and *Shh*, whereas distal lung morphogenesis is strictly dependent on Nkx2.1. Nkx2.1 in the neonatal lung controls development by regulating morphoregulatory target genes, the latter interactions may inevitably inhibit lung development, cellular differentiation, and production of pulmonary surfactant. Disruption of key factors such as Nkx2.1 potentially derails both ongoing morphogenesis and repair from the early stages of branching morphogenesis through alveolarization.

Fetal and neonatal lung development by these mechanisms can be influenced by endogenous and exogenous conditions such as inflammation and hormones such as corticosteroids [24].

Inflammation and Oxidative Stress as a Developmental Modulator in the Lung

The etiology of bronchopulmonary dysplasia (BPD), the most common chronic lung disease in the premature infant, may therefore be related to interactions between untimely or spatially inappropriate signaling that arises from injury [e.g. inflammatory mediators] with alterations in morphogenetic signaling and transcriptional pathways that control normal development and repair. It has been proposed that the main pathway through which the effects of various insults, such as antenatal infection, surfactant insufficiency (volutrauma), or oxygen toxicity are translated into lung injury, is 'inflammation'. If inflammation is present in BPD what are the potential linkages connecting inflammation and morphogenesis? Decreased expression of Nkx2.1 has been documented in the lungs of neonates who died with BPD [25]. TNF-α, which is abundantly expressed in the lungs of preterm neonates at risk for BPD, negatively regulates Nkx2.1 gene expression [26]. The most direct evidence for a functional linkage between inflammatory mediators and developmental pathways comes from transgenic mouse studies. Alveolar hypoplasia can be experimentally induced in transgenic mice with lung-specific ectopic and/or overexpression of TNF-α and IL-6 [27]. Taken together these observations suggest that prolonged exposure to a pro-inflammatory environment during early development has a direct effect on the development of the distal airways in preterm infants of low gestational age and may induce alveolar hypoplasia. This finding provides a potential mechanistic explanation for phenotypic differences between 'new' vs. 'old' BPD or BPD in extremely-low-birth-weight vs. that in low-birth-weight infants.

Inflammation and the presence of activated phagocytes release a large amount of oxygen radicals and pro-

teases. Over the last decade, accumulating data have indicated that oxidative stress is involved in the development of BPD [28]. Exposure of newborn rats to hyperoxia impairs alveolarization and vessel growth, causing abnormal lung structure that persists during infancy. Lipid and protein peroxidation products have been found increased in preterm infants developing BPD. New data have also shown that free radicals are second messengers and signal transducers in biologic processes [29]. One example is the action of nitric oxide (NO), which is a free radical and may react with the superoxide radical to form toxic peroxynitrite ($ONOO^-$) but NO is also a messenger molecule with unique signaling properties [29]. NO can restore distal lung growth in infant rats after neonatal hyperoxia [30].

Inflammation and the presence of neutrophils lead to the release of enzymes such as elastase and matrix metalloproteinases that disrupt the lung extracellular matrix. The extracellular matrix is essential for the normal alignment and differentiation of pneumocytes and pulmonary capillaries. The increased ratio of MMP over tissue inhibitor of metalloproteinase (TIMP) in preterm infants bronchoalveolar lavage can indicate alteration of lung development by extracellular matrix disruption [24].

Inflammation further activates the ubiquitous transcription factor NF-kappa B, which mediates many of its biological effects. Muraoka et al. [31] observed that experimentally induced perturbations in NF-kappa B gene expression disrupted epithelial-mesenchymal interactions, and resulted in abnormal lung morphogenesis with reduced growth and branching. Thus NF-kappa B can modulate both inflammatory and morphoregulatory genes, thereby establishing a tight operational and functional linkage between inflammation and development. These data provide examples of potential interactions between mediators of injury and those of normal morphogenetic pathways in the development of the lung (fig. 2).

Inflammation and Oxidative Stress as a Developmental Modulator in the Brain

The inflammatory response is a common pathway of generating injury to the white matter between hypoxic-ischemic and infectious insults [32]. The human fetus is able to generate inflammatory responses by 16–22 weeks of gestation. The inflammatory signals are propagated across the intact or ruptured blood-brain barrier to the brain by pro-inflammatory cytokines, prostaglandins and lipopolysaccharides. Subsequently, microglia are stimulated to release cytokines, oxygen free radicals and trophic factors which will influence the brain in various ways [33]. In particular, inflammatory events occurring prenatally are strongly correlated with white matter injury and the association of premature rupture of the membranes and perinatal infection yields a very high risk for white matter injury [34]. The systemic inflammatory response is indicated by a markedly elevated level of inflammatory cytokine, IL-6 in fetal plasma [35]. Infants with white matter injury were found to have increased IL-6 and TNF-α cord blood [36] and CSF levels [37]. Importantly, the IL-6 family of cytokines interfere with normal development by inducing differentiation of the developing bipotential oligodendrocyte precursor cells into astrocytes and away from the differentiation into a mature oligodendrocyte [38]. This may in part explain the marked astrocytosis and delay in myelination seen in diffuse white matter damage of the very preterm infant [39] (see below).

Kadhim et al. [40] illustrated that an inflammatory reaction, characterized by macrophage infiltration and high levels of IL-1β and TNF-α was present in immunostaining of preterm brain tissue with white matter injury. While cortical and other neuronal structures in brains with white matter damage did not display noticeable pathological anomalies, strong cytokine immunoreactivity was detected in many neurons in the neocortex, hippocampus, basal ganglia and thalamus, which indicates potential alteration of cortical development associated with the inflammatory response [41]. Potentially affected neurons in early development are those of the subplate. Subplate neurons express different neurotransmitters (e.g. GABA, glutamate), neuropeptides (Reelin) and growth factors (BDNF, PAF) receive synapses and make connections with cortical and subcortical structures. These neurons play several important roles during brain development including: (1) they produce axons for the internal capsule which will serve as guiding axons for axons originating from neurons in layers V and VI; (2) between 25 and 32 gestational weeks, they produce axons for the corpus callosum; (3) they act as the waiting zone for thalamocortical axons (with which they establish synapses) before they invade the cortical plate and reach layer IV.

Specific immunocytochemical markers (e.g. CD68) have identified marked increases of activated microglia in diffuse white matter injury [42]. Microglia are already widely dispersed throughout the immature white matter by 22 weeks' gestation. These cells are fully capable of producing potentially toxic inflammatory mediators, free

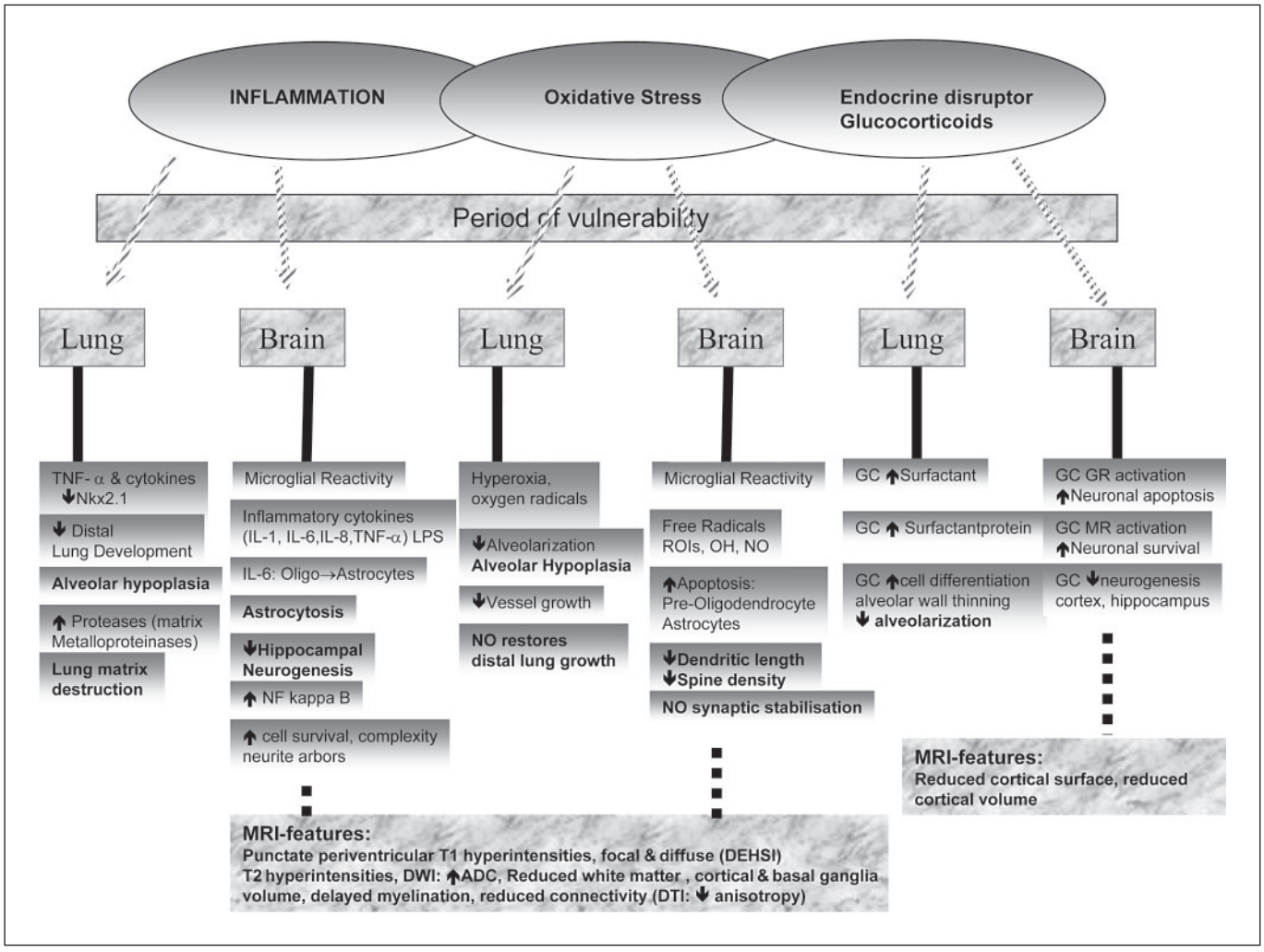

Fig. 2. Schematic representation of the factors involved in developmental modulation in lung and brain development including specific features of neuroimaging by advanced MRI.

radicals and reactive oxygen intermediates [43]. The phagocytic activity of microglia and their capacity for oxidative mediated injury are potently enhanced by inflammatory mediators (IFN-γ, TNF-α, IL-β and bacterial lipopolysaccharide LPS) [44]. Presence of activated microglia inducing cell death in immature white matter both in preoligodendrocytes as well as in astrocytes has been widely confirmed [45, 46].

Oxidative stress on neuronal membranes, detected as isoprostanes, also has direct effects on neuronal growth with a reduction of dendritic length and dendritic spine density which in the adult is transitory [47] but might be different in the developing brain. Pro-inflammatory cytokines such as IL-6 and TNF-α further have been shown to impair hippocampal neurogenesis [48]. Based on these findings, oxidative stress induced by the protracted hypoxia and the subsequent re-oxygenation phase occurring frequently in the preterm infant with respiratory problems is another mechanism by which developmental events can be altered. The matrix metalloproteinases (MMPs) are a family of extracellular proteases implicated in brain development and disease [49]. In many adult inflammatory and ischemic disorders MMPs are highly expressed in the CNS but their role in altering brain development is not yet clear.

These studies indicate that there exists a developmental period during which the lung and brain share a developmental vulnerability to injury by inflammation which

may lead to permanent alteration of structure and function through a concomitant alteration of the developmental program (fig. 2).

Glucocorticoids as a Developmental Modulator in the Lung

Over the last three decades, the effects of antenatal glucocorticoids (GCs) on fetal lung maturation and the pulmonary surfactant system have been a topic of intense scientific and clinical interest [50, 51]. In humans GCs primarily stimulate the synthesis of surfactant phospholipids by inducing de novo synthesis of fatty acids. Additionally, GCs increase the expression of surfactant proteins B, C and D by increasing the transcription of the genes [52]. On a structural level GCs promote lung cell proliferation, the differentiation of type II alveolar epithelial cells and the thinning of the alveolar walls mediated by growth factors such as TGF-β, VEGF and others. These changes occur with physiological levels of GCs which increase in the fetus during the last trimester of pregnancy. In earlier developmental periods formation of alveoli can be largely prevented by GC treatment which accelerates alveolar wall thinning but inhibits outgrowth of new interalveolar septa [53] which results in decreased alveolar number [54]. These changes of decreased alveolarization can persist and lead to definitive alteration of lung development [55]. Interestingly, these changes induced by synthetic GCs seem to be dependent in part on the type of synthetic GC used, with hydrocortisone affecting alveolar growth less than dexamethasone [56] (fig. 2).

Glucocorticoids as a Developmental Modulator in the Brain

GCs have powerful brain-programming properties [57]. One of the most intensively studied programmed systems is the hypothalamic-pituitary-adrenal (HPA) axis. The axis mediates the release of GCs to diurnal cues and stress. GCs act predominantly via intracellular receptors which function as ligand-activated transcription factors. There are two receptor subtypes: the lower affinity glucocorticoid (GR) and higher affinity mineralocorticoid (MR) receptors.

GCs are essential for many aspects of normal human brain development. They affect most regions of the developing brain and regulate neurogenesis and neuronal survival. Experiments describing the effects of injecting pregnant rats with dexamethasone (DEX) have shed some light on the involvement of prenatal GC exposure in fetal programming of the brain [58]. At conventional therapeutic doses DEX is a potent GR but not MR agonist. Decreased brain weight is a well-established consequence of perinatal DEX administration. Prenatal DEX exposure in late gestation influences brain development altering the induction of nuclear transcription factors such as c-*fos* and AP-1 that regulate brain cell differentiation with long-term c-*fos* induction, resulting in a subsequent decline in brain cell number. Even at doses that were devoid of lasting effects on somatic growth DEX elicited deficits in the number and size of neural cells with the largest effect in the cerebral cortex [59]. Recent studies using dosages similar to or below those used for lung maturation in preterm infants indicate that, during critical developmental periods, DEX administration evokes lasting alterations in neural cell numbers and synaptic function in forebrain regions with a predilection for the male vs. female brain [60]. In the hippocampus GR activation induces apoptosis of granule cells by increasing the ratio of the proapoptotic molecule Bax relative to the antiapoptotic molecules Bcl-2 or Bcl-x(L); the opposite effect is observed after stimulation of MR which enhances neuronal survival [61]. These are important mechanisms to help understand the differential effects of different corticosteroids used in therapeutic interventions.

Under normal conditions access of maternal endogenous GC to the fetus is low and this is related to the expression of 11β-hydroxysteroid dehydrogenase in the placenta, which protects the fetus from high maternal GC concentrations. This enzyme though has a low affinity for synthetic GCs such as bethamethasone and DEX that pass rapidly from the mother to the fetus.

Several clinical conditions potentially expose the fetus and the preterm newborn to GCs. Firstly maternal stress and placental insufficiency can lead to fetal exposure of higher cortisol levels [62], secondly, induction of lung maturation achieved by synthetic GC administration antenatally and thirdly postnatal GC treatment for chronic lung disease. From the mid-1980s, postnatal corticosteroids were increasingly prescribed for the prevention or treatment of chronic lung disease (CLD), supported by evidence of benefit on some short-term outcomes, including earlier weaning from mechanical ventilation and a reduction in CLD [63–66]. CLD and prolonged mechanical ventilation, both tightly related to inflammation, are themselves risk factors for a developmental insult to the brain in preterm infants as illustrated above. GCs as po-

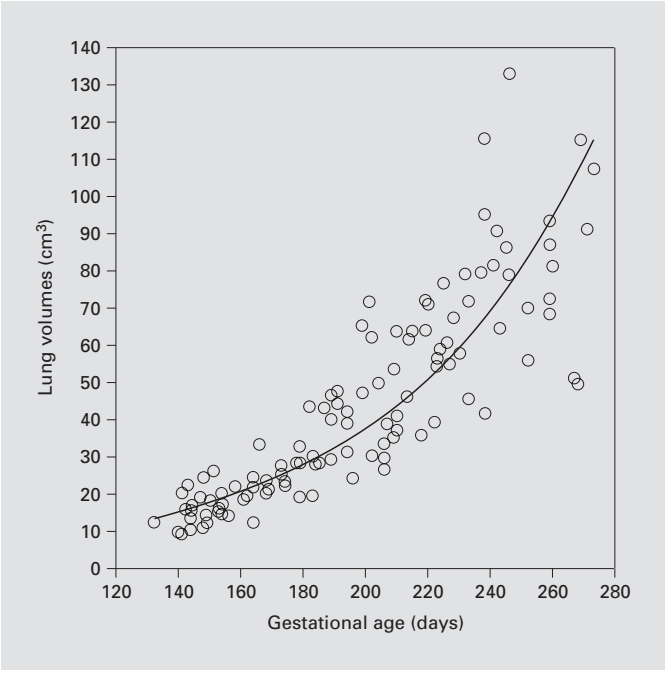

Fig. 3. MR lung volumetry results of 106 fetuses, with normal history or with abnormalities not associated with restricted lung growth. An exponential regression curve showed the best fit (r^2 = 0.81). There is only a minimal growth of lung volumes between 140 and 175 days, at 20 and 24 GW, respectively. With permission from Kasprian et al. [73].

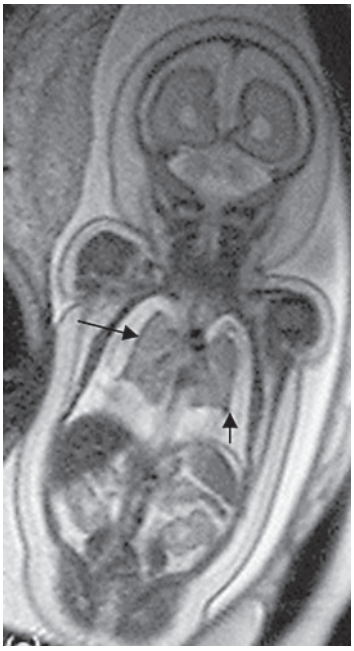

Fig. 4. Coronal T2-weighted sequences of a fetus at 27 GW with severe pulmonary hypoplasia and hydrops. Measured lung size was 11.65 cm^3 and size of the pleural cavity was 54.84 cm^3. The signal intensity of the fetal lung appears markedly hypointense. Arrows indicate lung parenchyma. With permission from Kasprian et al. [73].

tent anti-inflammatory agents though were hoped to reduce the systemic effects of inflammation and oxidative stress for the developing organism. However, several randomized controlled trials have been reported with an increase of neurodevelopmental disabilities associated with postnatal corticosteroid use [67–70]. Similar reports also had been published earlier for the effects of multiple doses of antenatal corticosteroids [71]. Most of the studies have been done with synthetic DEX, which is a potent activator of GR rather than MR. Hydrocortisone on the other hand has higher MR affinity which might prove neuroprotective. A recent study looking at outcome after treatment of CLD with hydrocortisone indicates no difference in neurodevelopmental outcome for hydrocortisone treatment [72].

Steroid hormones are therefore another environmental factor operating in early life that potently affect the developing organism altering structure and function (fig. 2).

Visualization of Developmental Disruption by Lung Imaging

MRI is a new noninvasive method to study human lung growth during the second and third trimester. The excellent tissue contrast of MRI allows a detailed structural assessment of the fetal lung [73]. Using different ultrafast MRI sequences important data concerning the characteristics of the pulmonary parenchyma can be obtained [74]. Fetal MR volumetry allows identification of lung growth and diagnosis of hypoplasia. The evaluation of signal intensities using different MR sequences provides information about the tissue maturational status of the fetal lung and allows identification of pulmonary tissue pathologies. The median pulmonary volume at 20 weeks' gestational age was shown to be around 10.17 cm^3. Values then increase exponentially after 24 weeks' GA, showing a considerable variability of lung volumes between 51.16 and 132.96 cm^3 after 35 weeks' GA (fig. 3) [73]. Several developmental processes may account for the changes observed in the signal intensities on T2-

weighted lung imaging. In parallel with the increase in future airspace and permanent secretion of lung fluid, an accumulation of free protons and the decrease of the water binding hyaluronic acid fraction could be responsible for the changing appearance of the developing lung on T2-weighted sequences, which has a large interindividual variability [75]. Pulmonary hypoplasia may be the endpoint of many processes that influence human lung development. Pathologically, pulmonary hypoplasia is defined by a reduction of total size, lung weight/body weight ratio, radial alveolar count and DNA content. Marked reduction of signal intensities and lung volumes [76–78] are characteristic findings in fetuses with pulmonary hypoplasia (fig. 4). After GC administration for lung maturation by which the alveolar size increased and interlobular septal volume decreased [79] parallel changes are observed in T2-weighted imaging with a brighter signal (T2 increase) [73].

Alterations in lung volumes calculated from lung MR imaging together with changes in MR signal intensities can detect in vivo disruption of lung development.

Visualization of Developmental Disruption and Plasticity by Neuroimaging

Neonatal sonography is still the best bedside technique to image the neonatal brain. Leviton and Paneth [80] postulated in 1990 that ultrasonographic white matter echodensities and echolucencies in low-birth-weight infants predicted later handicap more accurately than any other factor. Since then many studies have shown neurodevelopmental delay in preterm infants with normal postnatal ultrasound scans [81]. Unlike intraventricular hemorrhage or cystic periventricular leukomalacia, developmental disruption in both white matter and cortical gray matter have no focal appearance. Diffuse white matter injury by its specific pathological features might be difficult to diagnose by ultrasound. Inder et al. [82] recently compared early ultrasound assessment with conventional MRI at term age in a nonselected cohort of preterm infants, and found a low predictive value of ultrasound for white matter lesions that were apparent on MRI. One typical conventional MR imaging pattern of white matter injury consists of punctate periventricular areas of signal hyperintensities on T1-weighted images (fig. 5) and signal hypointensities in T2-weighted images [83, 84]. The neuropathological correlate of these signal abnormalities may result from some hemorrhagic components of the lesions but more likely represents the cellular reaction of glial cells and macrophages, which contain lipid droplets [85]. Another feature of chronic white matter alteration in conventional MR imaging in the immature brain is characterized by a persistent high signal intensity of the white matter in T2-weighted images (fig. 6). In several studies diffuse excessive high signal intensity (DEHSI) in the cerebral white matter on T2-weighted imaging was present in 40 to 75% of low-birth-weight preterm infants imaged at term [81]. Its association with very early gestational age, was recently demonstrated in a cohort of premature infants studied by conventional MRI at term [86]. This study further illustrated the specific pattern of global alteration of the very immature brain at term with marked reduction of white matter volume, T2-weighted hyperintensity of white matter, delayed myelination, ventriculomegaly and significantly enlarged subarachnoid spaces indicating cortical atrophy. In a logistic model major risk factors for this abnormality were perinatal infection particularly maternal fever and hypotension with inotrope use [86]. These diffuse white matter alterations were further associated with higher CSF IL-6, and TNF-α levels which confirms the high likelihood of inflammatory processes at the origin of these specific diffuse cerebral alterations in very immature infants [87]. Similar correlation with image abnormalities were found for lipid (8-isoprostane, malondialdehyde) and protein (protein carbonyls) peroxidation products in CSF of preterm infants [88].

Imaging techniques to study both acute brain injury as well as the brain's potential for plasticity are being used increasingly to study immature white matter. The most promising imaging techniques are diffusion-weighted (DWI) and diffusion-tensor (DTI) imaging which measure the self-diffusion of water. The two primary pieces of information available from DWI studies – water apparent diffusion coefficient (ADC) and diffusion anisotropy measures – change dramatically during development, reflecting underlying changes in tissue water content and cytoarchitecture [89]. The above-described typical white matter changes in preterm infants at term demonstrating higher ADC values in the area of T2 hyperintensities [90, 91] which most likely is related to disruption of normal microstructure with potential neuroaxonal loss (with loss of associated pre-oligodendrocytes). Quantitative measures of diffusion at term among premature infants with perinatal white matter alterations, when compared to preterm infants without white matter injury, showed lower anisotropy values, an expression of altered white matter fiber connectivity in the central periventricular white matter and also in proximal fibers of the

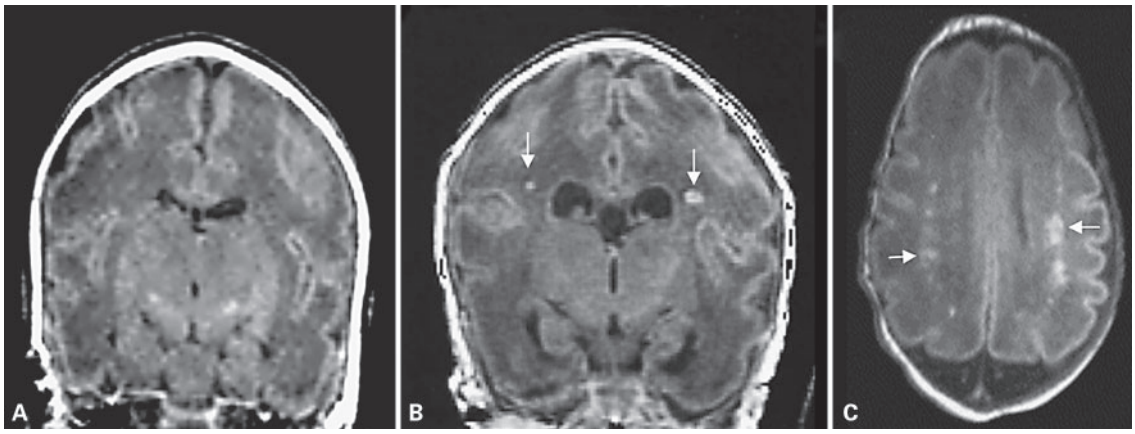

Fig. 5. Conventional T1-weighted MR images in coronal (**A**, **B**) and axial plane (**C**). A normal preterm infant at 31 weeks GA; **B** and **C** illustrating bilateral periventricular lesions with high T1 signal intensities in a preterm infant of 31 weeks GA (white arrows).

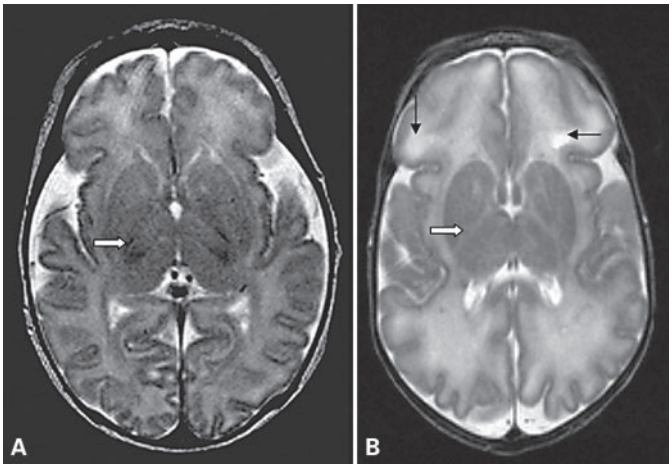

Fig. 6. Conventional T2-weighted MRI of a normal full-term infant (**A**) with thin area of low signal in the T2-weighted MRI corresponding to myelin deposition in the posterior limb of the internal capsule (white arrow). **B** Corresponding T2-weighted MRI in an ex-preterm infant of 25 weeks GA imaged at 40 weeks GA, with severe bronchopulmonary dysplasia showing diffuse white matter lesions (black arrows) and missing signal change in the posterior limb (white arrow) of the internal capsule, indicating delay in myelination.

posterior limb of the internal capsule [92]. Long-term follow-up of preterm infants with DTI have shown distinct changes in cerebral connectivity in both the corticospinal tracts and commissural fibers [93]. The use of DTI allows three-dimensional reconstruction of white matter connectivity which might become an important tool to assess abnormalities in cortical connectivity and structural and functional plasticity [94, 95].

Another recent imaging development is 3D-MRI, combined with image post-processing techniques, which allows volumetric assessment of brain development and an absolute quantitation of myelination and cortical development [96, 97]. In premature infants with white matter injury the volume of myelinated white matter at term as well as the volume of cortical gray matter was significantly lower with a compensatory increase in CSF [98] (fig. 7). In a recent population study, similar volumetric changes of overall brain development in preterm infants were confirmed with significant reduction of myelinated white matter and cortical gray matter in preterm infants compared to full-term infants with a reduction also of deep nuclear gray matter (basal ganglia) most pronounced in the lowest gestational ages. There was a significant relationship between severity of respiratory illness and the deep nuclear gray matter volumes indicating developmental disruption at multiple levels [99]. Neuropathological examination of cerebral cortex in preterm infants revealed cortical dysplasia in cortical areas overlaying white matter destruction [39]. These abnormalities of cortical development are found secondary to disturbances of afferent input to and efferent output from areas of the cortex by disruption of the respective white matter axons [39]. Long-term follow-up studies of preterm infants have confirmed the permanent character of these disruptive/adaptive changes in brain development. Recent evaluations of 8-year-old former preterm infants with volumetric brain assessment showed persistence of

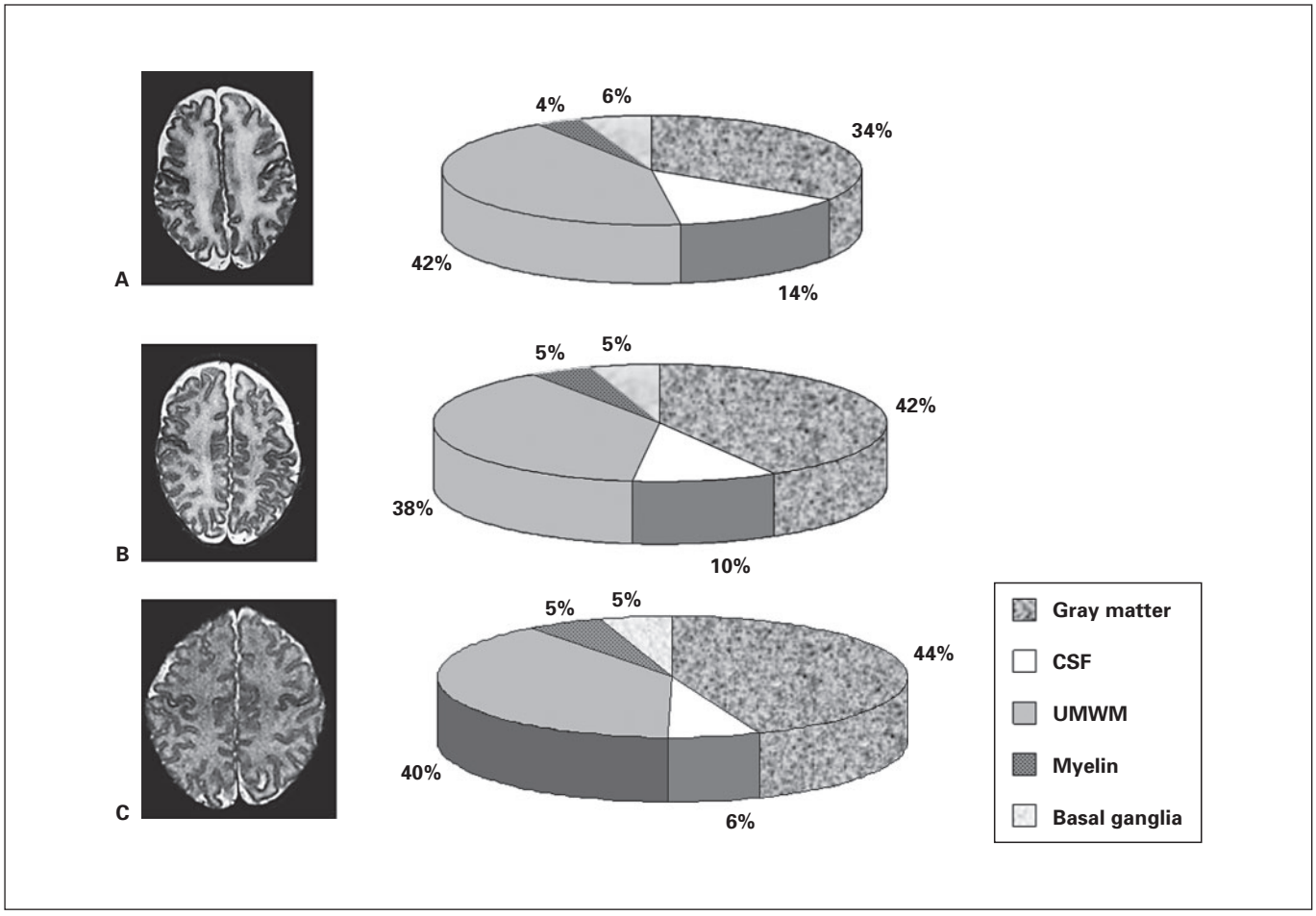

Fig. 7. Figure illustrating the effects of prematurity (**B**) and white matter injury (**A**) on subsequent brain development at term with a significantly lower cortical gray matter volume, lower myelinated white matter and higher CSF volumes determined by 3D-MRI with post-acquisition image analysis in a group of preterm infants with perinatal white matter injury compared to control preterm and full-term infants (**C**). With permission from Inder et al. [98].

cortical gray matter reduction accompanied with a reduction in the volume of the hippocampus which correlated with cognitive scores indicating long-term functional consequences [100] (fig. 8). Both cortical volume and cortical thickness were shown to be reduced in 15-year-old adolescents who had been born prematurely [101].

Dramatic changes in brain volumetric assessments have also been found after exposure to corticosteroids. Multiple antenatal doses of corticosteroids were associated with a marked reduction in cortical surface at birth [102] and postnatal dexamethasone treatment resulted in a 30% reduction of cortical gray matter volume without any changes in white matter characteristics [103] (fig. 9). As outlined above, different corticosteroids might have different modulatory actions on brain development. It is interesting to note that a recent study on the long-term effects of hydrocortisone treatment for neonatal chronic lung disease did not show any long-term changes in cortical and hippocampal development with no effects on neurodevelopmental outcome [100]. This opens up the possibility to consider hydrocortisone treatment for chronic lung disease as the inflammatory processes of CLD remain a potent risk factor for abnormal brain development. A recent study by Doyle et al. [67] indicates that for patients with high risks of CLD (>65%) corticosteroid treatment was associated with a reduction in death or cerebral palsy.

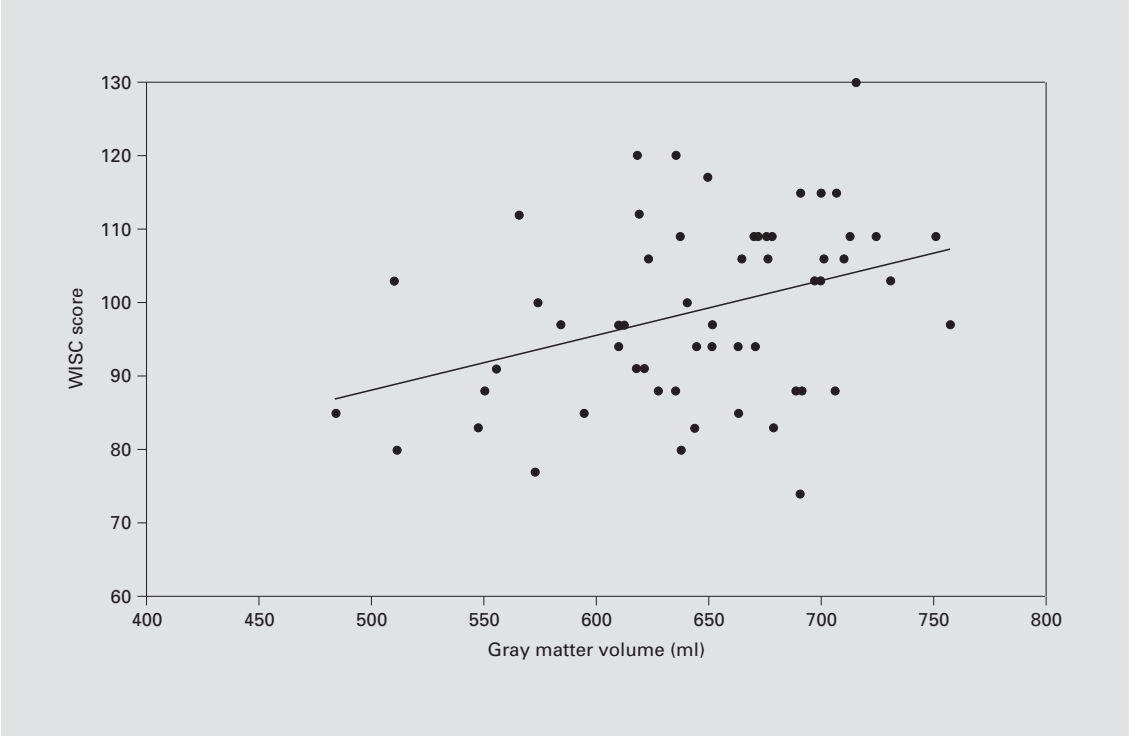

Fig. 8. Correlation of cortical gray matter volume and neurocognitive scores (WISC) at the age of 8 years in preterm infants. With permission from Lodygensky et al. [100].

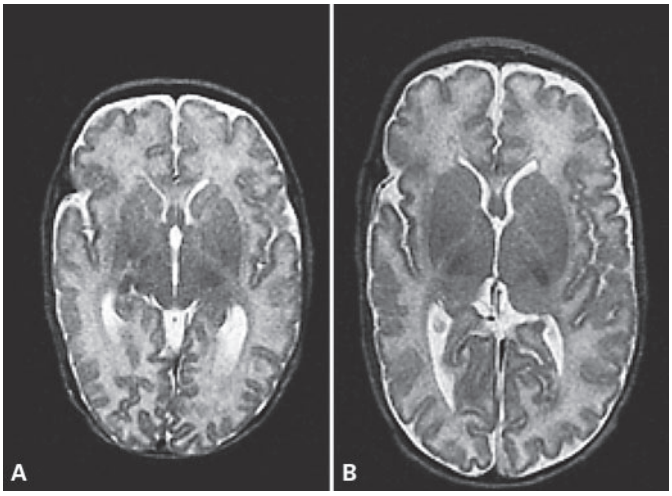

Fig. 9. Axial T2-weighted magnetic resonance images from a premature infant at term treated with systemic dexamethasone for neonatal chronic lung disease (**A**), and a premature infant at term who never received dexamethasone (**B**). With permission from Murphy et al. [103].

Conclusions

The progressive understanding of the mechanisms of developmental disruption and developmental plasticity in different organs may help explain the long-term effects of prematurity and its associated environmental cues important for organ development. Developmental disruption and plasticity occurs in both lung and brain and is tightly linked to events inducing inflammation, oxidative stress and endocrine disruption. Future studies on pulmonary and neurological outcome in premature infants will have to focus not only on lung and brain injury prevention but enhancement of developmental plasticity.

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