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Fetal Inflammatory Response and Brain Injury in the Preterm Newborn

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Abstract

Preterm birth can be caused by intrauterine infection and maternal/fetal inflammatory responses. Maternal inflammation (chorioamnionitis) is often followed by a systemic fetal inflammatory response characterized by elevated levels of pro-inflammatory cytokines in the fetal circulation. The inflammation signal is likely transmitted across the blood-brain barrier, and initiates a neuroinflammatory response. Microglial activation has a central role in this process, and triggers excitotoxic, inflammatory, and oxidative damage in the developing brain. Neuroinflammation can persist over a period of time and sensitize the brain to subinjurious insults in early and chronic phases, but may offer relative tolerance in the intermediate period through activation of endogenous anti-inflammatory, protective, and repair mechanisms. Neuroinflammatory injury not only destroys what exists, but also changes what develops.

Keywords

infection; inflammation; anti-inflammation; neuroinflammation; fetus; brain; injury; protection; repair

Systemic inflammatory conditions outside the fetal brain can induce injury in the fetal brain and modulate its response to various insults. In this paper, we review the evidence for the relationship between the fetal inflammatory response and brain injury, and pathomechanisms by which this injury can occur, with main emphasis on brain damage in preterm newborns. We also shed light on the concept of altered brain development and response to injury in the setting of fetal inflammation, and the potential for protection and repair. We acknowledge that our overview is selective rather than all-inclusive. More comprehensive discussion of recent progress in the field of fetal inflammation and perinatal brain injury is available elsewhere.[1–4]

Intrauterine Infection, Inflammation, and Preterm Birth

The fetus, placenta, and fetal membranes co-exist in close proximity to the microbial flora in the lower genitourinary tract. For more than four decades, microbial infections were suspected to play a role in the etiology of preterm labor, and the complications and

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outcomes of prematurity.[5–8] Recent summaries of this scenario are available in the current obstetric literature.[9–11]

Most recently, a large multicenter cohort of around 1500 extremely low-gestational- age newborns (ELGANs, <28 weeks gestation) was recruited. Extensive data were collected on placental histology and bacteriology, neonatal biomarkers, and neonatal brain, lung, and eye outcomes over a 2-year follow-up period.[12–18] Placental microbiology studies revealed significantly higher rates of bacterial colonization in pregnancies that progressed to spontaneous preterm labor, compared with pregnancies delivered for preeclampsia as an initiator for their preterm delivery.[17] In particular, colonization of placental tissues with 2 or more microorganisms was associated with a significantly increased risk for preterm labor as an initiator of delivery compared with colonization with one or no microorganism.[18]

Bacteria and bacterial products activate toll-like receptors on the surface of inflammatory cells in the decidua and placental membranes, resulting in the release of proinflammatory chemokines and cytokines from these cells and the initiation of a local inflammatory reaction in the placenta.[19,20] Chorioamnionitis is the histological condition of (maternal) neutrophil infiltration of the chorion and amnion. Umbilical vasculitis is the (fetal) neutrophil response in umbilical and chorionic plate vessels.[13,21] Activation of inflammatory cells in the placenta and the spread of proinflammatory molecules appear to propagate chorioamnionitis and fetal vasculitis.[22] Viral infections can also act as initiators of histologic chorioamnionitis and fetal vasculitis.[23] These data add to the growing evidence linking placental and fetal infection and inflammation to preterm labor and preterm birth.[11]

Not all prematurity is equal with regard to infectious/inflammatory characteristics. A clinically helpful classification of pregnancy conditions that lead to preterm delivery prior to 28 weeks of gestation divides disorders of pregnancy into 2 groups.[16] The first includes placental histology patterns associated with aberrations of placentation such as decidual hemorrhages or fibrin deposition, placental infarcts, increased syncytial knots, thrombosis of fetal stem vessels, and a lack of microorganisms and markers of inflammation. This pattern is associated with preeclampsia and fetal indication/intrauterine growth restriction, leading to preterm delivery. The second group includes placental patterns associated with intrauterine infection/inflammation, such as inflammation of the chorionic plate or of the fetal membranes, fetal stem vessels, or umbilical cord vasculitis, or placental microbe recovery. This pattern is associated with spontaneous preterm labor, prelabor premature rupture of membranes, placental abruption and cervical insufficiency. Keeping initiators of preterm delivery separate is important for our scenario because they might carry different risk information for neonatal[24] and longterm neurocognitive outcomes.[25]

Intrauterine Infection, Inflammation, and Preterm Brain Injury

Infants with postmortem bacteremia are much more likely to have histologic white matter damage than infants whose blood cultures were sterile.[26] Because no microbes were identified in these babies' brains, the authors of this seminal study postulated more than three decades ago that a circulating, noninfectious product of inflammation or endotoxin from bacteremia might lead to brain damage. Since then, evidence has accumulated in support of the concept that infection distant from the brain and exposure to endotoxins and/or inflammatory cytokines can damage the developing fetal brain.[1,2,27–44]

The proinflammatory response in the placenta involves the activation of a complex cytokine network at the chorio-decidual interface, including mediators that transmit inflammatory signals between maternal and fetal gestational tissues.[45] Chorioamnionitis with funisitis is associated with umbilical cord endothelial cell activation, with upregulation and shedding of cell adhesion molecules,[46,47] and with a systemic elevation of interleukin-6 levels.[48,49] This

rapid innate immune response can activate fetal leukocytes,[50,51] which is, in turn, associated with neonatal white matter damage depicted on magnetic resonance images.[52] We speculate that fetal white cell activation[53] and the interaction between the innate and adaptive components of the immune system[54] play a prominent role in fetal/neonatal white matter damage.

One important inference based on these assumptions is that neuroinflammation as a pathogenetic mediator is not a single hit in time, but a process extended over a period of time (Figure).[55] An ongoing process involving T-cell-related immune mechanisms, together with cross-links to other systemic systems (eg, the coagulation[56] and complement systems)[57, 58] is a much more plausible scenario (depicted as scenario A in the Figure) than a single-hit model (scenario B) for the fetal systemic inflammatory response as an initiator of the multiorgan system dysfunctions seen in exposed fetuses.[10,59]

It is often purported that cerebral hypoperfusion as a consequence of systemic hypoperfusion and shock is one pathomechanism by which the fetal brain can be damaged by in the setting of systemic inflammation. However, this concept is not well-supported by studies of systemic hypotension as a risk factor for neonatal brain damage.[60,61] Experimental models of antenatal systemic exposure of the ovine fetus to inflammation also do not suggest that circulatory insufficiency contributes to the associated damage seen in the developing white matter.[62–64] Taken together, these data suggest that inflammatory processes in and of themselves play an important role in perinatal brain damage causation in preterm newborns, whether circulatory disturbances are present or not.

From System to Brain

An intact blood-brain barrier separates the brain parenchyma from circulatory molecules that may alter the homeostasis of the central nervous system. Tight junctions in barrier interfaces in the developing brain are impermeable to even small lipid insoluble molecules.[65–67] Nevertheless, there are multiple putative mechanisms by which the brain can sense inflammatory signals in the systemic circulation.[67,68]

Circumventricular organs represent areas in the brain that are devoid of the blood-brain barrier. Here, large molecules such as peptides, cytokines, and bacterial products in the circulation can come in direct contact with cellular elements in the central nervous system.[69] These areas possess a population of antigen-presenting cells and macrophages that can interface with many of these circulating molecules and activate a local inflammatory response comparable to the activation of the innate immune response system elsewhere in the body. Toll-like receptors for lipopolysaccharide and receptors for interleukin-1 have been identified on the surface of these cells in the circumventricular organs.[70,71] Activation of these receptors triggers a nuclear factor NF-kB-mediated cascade that releases in a paracrine fashion a number of cytokines and chemokines that can propagate the inflammatory signal to neighboring cells in the central nervous system.[72]

Alternatively, direct access into the central nervous system by inflammatory molecules and/or activated white blood cells can be facilitated by breakdown of the blood-brain barrier in the setting of hypoxia-ischemia/reperfusion injury,[73] or through leaking of the blood-brain barrier in the setting of peripheral inflammatory pain signaling through the vagal nerve.[74] Cytokines also may gain access into the brain through carrier-mediated transporter mechanisms across the blood-brain barrier. These mechanisms however appear to be of limited capacity and are rapidly saturated.[75] Another mechanism for inflammatory signaling across the blood-brain barrier involves a role for the blood-brain barrier itself as a sensor organ for the central nervous system.[68] When cytokines in the circulation bind to their receptors on the luminal side of endothelial and other cells associated with the blood-brain

barrier, prostaglandins are released from the basal side of the blood-brain barrier and spread as a paracrine inflammatory signal throughout the adjacent brain parenchyma.

The exact contribution of any of these mechanisms in the setting of fetal inflammation remains unknown. To our knowledge, only one group of colleagues has embarked upon this endeavor.[76–78] They have most recently summarized their results (together with a most interesting hypothetical expansion toward neurologic disorders in adulthood), suggesting "that breakdown of normal blood-brain barrier function resulting in a short-lasting influx of blood borne molecules, in particular plasma proteins, may cause local damage such as reduction of brain white matter observed in some newborn babies, but may also be the mechanism behind some neurodegenerative diseases related to underlying brain damage and long-term changes in barrier properties".[79]

Microglia, Oligodendrocytes, and Neurons

Activation of microglia is one major characteristic of the neuroinflammatory response in the central nervous system.[34] Microglia are the only non-neural cells in the brain expressing toll-like receptor 4, the lipopolysaccharide receptor, and must be present in co-culture with oligodendrocytes for lipopolysaccharide-induced oligodendrocyte death to occur.[80] Microglial activation is considered crucial for excitotoxic, inflammatory, and free radical injury to cells in the developing central nervous system.[81]

Immature oligodendrocytes have been proposed also to be a main target of these injury mechanisms in the premature brain.[82–84] These cells may be particularly more vulnerable to developmental injury than their mature counterparts, a finding that helps explain the vulnerability of the premature brain to various insults.[85] A diffuse encephalopathy involving elements of the fetal grey matter, such as axonal tracts, neural progenitor cells, and neurons, is likely to be the underlying scenario of cognitive disability in premature infants in the setting of perinatal infection/inflammation.[86,87]

Inflammation as Modulator of Other Insults

In addition to direct injury mediated by the processes outlined above, the activation of the neuroinflammatory response can also sensitize the brain to the damaging effects of other insults, even when these insults do not cause much injury in and of themselves. For example, a degree of hypoxia-ischemia insufficient to result in overt brain injury caused massive brain injury when the insult was preceded by exposure to lipopolysaccharide in an immature rat model.[88]

Inflammation, however, can also induce a resistance to damage from insults to the immature brain.[89] This preconditioning effect appears to depend upon the timing of the exposure to the inflammatory stimulus in relation to the onset of the injurious insult to the immature brain. While enhanced vulnerability of the developing brain to hypoxic-ischemic insult was observed in 7-day-old rats both in the acute (4- to 6-hour) and the chronic (72-hour) phase after lipopolysaccharide administration, lipopolysaccharide reduced brain injury by 78% when administered 24 hours before the insult.[90] Similar preconditioning effects are present in other brain injury models as well.[20,89,91–94] These issues further illustrate the concept that perinatal brain damage is more like a dynamic process over an extended period of time rather than a sudden, short-lasting insult (Figure). Multiple cellular and molecular mechanisms are activated along the perinatal time continuum, each with its own particular influence on the various cellular and histological components of the developing central nervous system.[20]

Protection

Neuroinflammation induces secondary anti-inflammatory cascades.[95] Negative feedback mechanisms slow down the progression of inflammation and protect the central nervous system from the various injurious effects of neuroinflammation, thereby preventing extensive brain damage subsequent to inflammation.[96] At least part of such mechanisms appear to be orchestrated by what has been termed “neuro-immune crosstalk,” the information exchange between immune and brain cells.[97]

One important additional level of complexity in this scenario is provided by the hypothalamic-pituitary-adrenal axis, which might play a role as a major anti-inflammatory system in the central nervous system in the setting of systemic inflammation.[72] Endotoxemia induces a surge in plasma ACTH and cortisol levels,[98] and prostaglandin synthesis can mediate the response of the hypothalamus to systemic inflammation.[99] This hypothalamic-pituitary-adrenal activation has protective anti-inflammatory effects on the central nervous system in the setting of inflammation. For example, profound neurodegeneration was found after intracerebral lipopolysaccharide injection in animals pretreated with the glucocorticoid receptor inhibitor Mifepristone (RU486) compared with controls.[96] The extent to which the hypothalamic-pituitary-adrenal axis is involved in the anti-inflammatory effects in the setting of fetal inflammation in humans is still unclear. However, the relative adrenal insufficiency of sick preterm newborns[100] might help explain their vulnerability to inflammatory brain damage.

A detailed review of potential anti-inflammatory and immunomodulatory strategies to actively protect the preterm brain is provided elsewhere.[101,102] However, there is currently no established neonatal intervention that could supplement the only antenatal protective intervention (ie, exposure to glucocorticoid).

In addition to activating anti-inflammatory feedback loops, neuroinflammation can activate some of the endogenous neuroprotective mechanisms that might help decrease the extent of damage subsequent to inflammatory insult. For example, a number of bioactive lipid messengers are formed and released in the local milieu at the site of brain injury and ongoing neurodegeneration.[103] Neuroprotectin D1 is a messenger with anti-apoptotic properties that can inhibit upstream signaling of the apoptotic cascade.[104] Interleukin-1-beta enhances NPD1 synthesis,[105] and may offer cytoprotection to cells adjacent to the site of ongoing neuroinflammation.

Repair

Neuroinflammation can also activate endogenous repair mechanism. Mutual interactions between cytokines and neurotrophic factors characterize normal and disease states.[106] For example, the pro-inflammatory cytokines tumor-necrosis-factor and interleukin-6, usually considered damage initiators, can lead to the production of neurotrophins, such as brain-derived neurotrophic factor[107] and nerve growth factor,[106] respectively, by astrocytes in defined brain regions. Other recent studies suggest a role for macrophages in axonal regeneration,[108] and for immune-based regulation of hippocampal neurogenesis (in adults).[109] In essence, inflammation probably not only initiates damage but also provides regulatory help in limiting the damage. One possible inference in this context is that a window might be present to modulate fetal inflammatory responses subsequent to the onset of inflammation, with the goal of protecting and repairing the preterm brain after the onset of preterm brain injury.[82,110]

Summary and Conclusion

The fetal inflammatory response to intrauterine infection plays a crucial role the pathogenesis of preterm birth and preterm brain injury. A neuroinflammatory response in the fetal central nervous system secondary to fetal infection and/or systemic inflammation is a likely pathomechanism of damage to the developing brain. The concurrent activation of anti-inflammatory mechanisms can provide negative feedback loops and induce neuroprotective and perhaps even repair mechanisms in the developing brain. A major concept that deserves further development is that brain injury associated with fetal/neonatal inflammation is not a static, one-point-in-time event, but rather a progression of cellular and molecular cascades in the fetal brain that evolves over time (Figure). This is illustrated by the time-dependent dual effect of inflammation on the central nervous system, either to sensitize the developing brain to subinjurious insults, or to offer a preconditioning neuroprotective effect to various insults. A related evolving concept is that brain injury in the setting of systemic inflammation is not only a destruction of what exists, but also a change of what develops. A better understanding of the different faces of perinatal neuroinflammation will help design interventions to improve neurodevelopmental outcomes after preterm birth.

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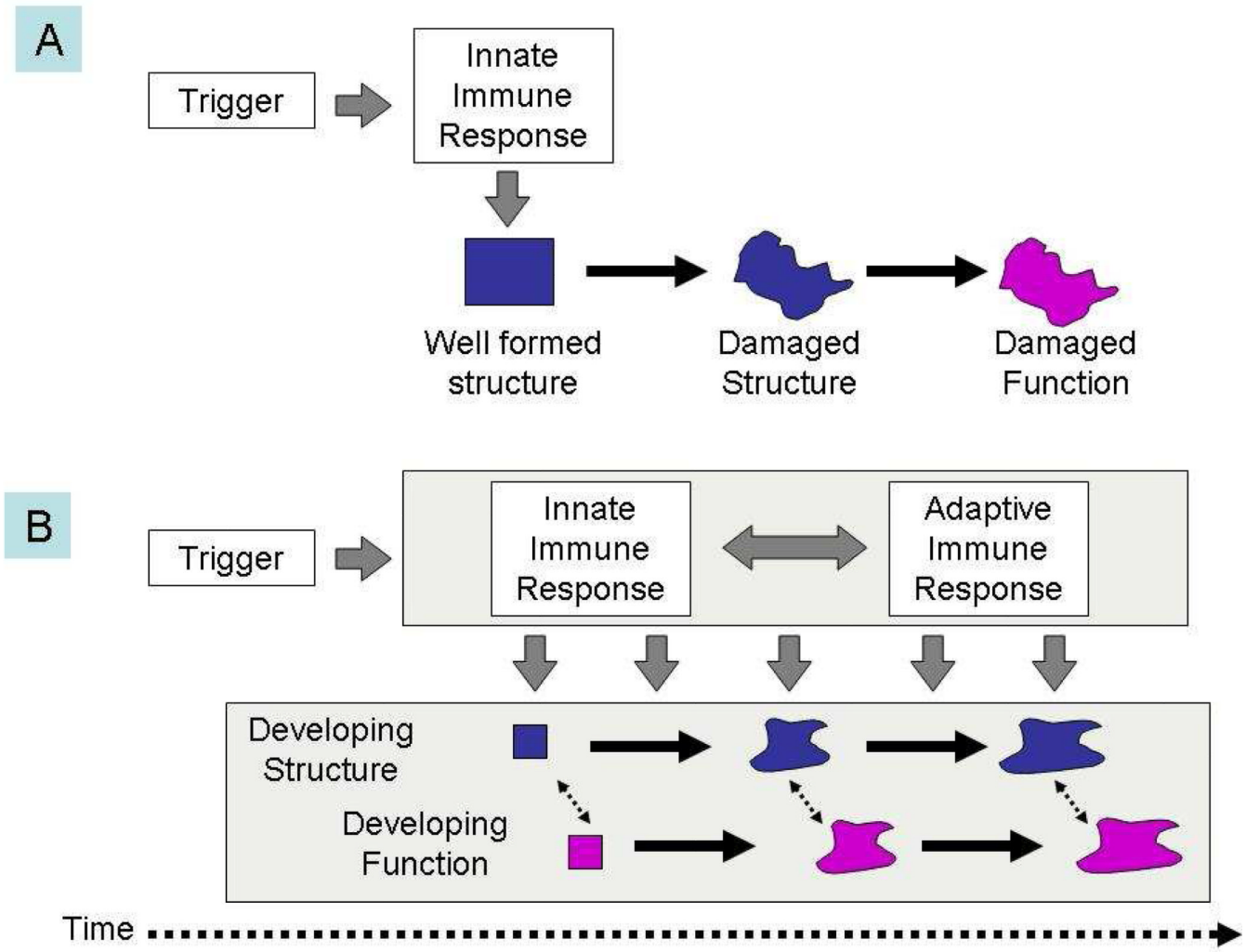

Figure 1.
The traditional scenario of perinatal brain injury (A) postulates that a single and rather short insult damages existing structure and leads to altered function. We propose the alternative view (B), which postulates that after an initial trigger has occurred, an ongoing interaction between innate and adaptive immune processes adversely affects the development of brain structure and function over an extended period of time.