

# Intermittent or sustained systemic inflammation and the preterm brain

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Exposure to perinatal infection and inflammation is associated with an increased risk for neonatal brain damage and developmental disabilities. In this integrated mechanism review, we discuss evidence in support of the contention that the preterm newborn is capable of intermittent or sustained systemic inflammation (ISSI), which appears to contribute more to adverse neurodevelopmental outcomes in preterm infants than does shorter duration inflammation.

The concept that noninfectious inflammatory stimuli contribute to perinatal brain damage dates back four decades (1). More than 15 y ago, this concept was expanded to help explain the relationship between contributors to preterm birth and perinatal brain damage (2,3).

Since then, the major new concept has been the role of sustained inflammation (4). The recent abundance of publications relevant to intermittent or sustained systemic inflammation (ISSI) prompts this update of recent progress.

## ISSI

### What Is Systemic Inflammation?

Although many infections are thought to be characterized by inflammation localized to a tissue or organ, some clinicians want to see leukocytosis before they make a diagnosis of appendicitis (5). The increase in number of immune cells and/or the increased concentration of inflammation-related proteins (e.g., C-reactive protein and proinflammatory cytokines) in the circulation is deemed evidence of systemic inflammation (6).

### What Is Chronic Systemic Inflammation?

A rapidly mounted systemic inflammatory response can be an effective defense against microbial invasion and should finally resolve (7). Failure of inflammation-resolution processes, however, leads to dysregulated and prolonged inflammation, which can damage organs and contribute to the development in adults of malignancies, chronic lung disease, rheumatoid arthritis, type 2 diabetes mellitus, heart disease, and such neurological disorders as stroke, Parkinson's disease, Alzheimer's disease, multiple sclerosis, and a diverse group of other neurodegenerative diseases (8).

### What Is ISSI?

We currently do not know if the systemic inflammation in very preterm newborns that predicts brain damage is intermittent or sustained. Until that knowledge becomes available, we consider it appropriate to use the term "ISSI" for this brain damage risk factor or indicator of other risk factors.

Both adjectives, intermittent and sustained, allow for the inflammation to eventually resolve. Some authors do not hesitate to eliminate this possibility when using the word "persistent" in describing among surgical patients what they call PICS, persistent inflammation, immunosuppression, and catabolism syndrome (9).

Some of what follows pertains to sustained inflammation in the brain and not necessarily in the circulation. We cite this literature in support of the concept of sustained inflammation and caution drawing inferences to what might be occurring in the blood when circulating indicators of systemic inflammation have not been measured.

### ISSI and Secondary Brain Damage

Closed head trauma can be followed by a prominent neuroinflammatory response (10). Although this might serve to assist in removal of debris and initiate repair, the possibility has also been raised that this phenomenon might contribute to ongoing "secondary" damage (11).

This phenomenon of secondary damage does not explain the systemic response that sometimes accompanies brain damage. This inflammation in the blood is most likely a reflection of inflammation that "spilled over" from the brain, or inflammation-provoking signals sent from the brain to the liver and the peripheral immune system (12). This inflammation in the blood following brain damage might be merely an indicator of the damage already done. On the other hand, the systemic inflammation might contribute to "secondary damage". A systemic anti-inflammatory approach to reducing secondary damage appears promising (13).

### ISSI and Tertiary Brain Damage

Tertiary brain damage is defined as "injury caused by long-persisting processes following brain insult that worsen

Note: Pierre Gressens, MD, PhD, served as the editor-in-charge for this paper.

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Received 26 June 2013; accepted 13 September 2013; advance online publication 15 January 2014. doi:10.1038/pr.2013.238

outcome, predispose to further injury, or prevent repair/regeneration” (11,14). One possible example comes from the observation that years after preterm birth, children who developed cerebral palsy had elevated tumor necrosis factor (TNF)- $\alpha$  concentrations in their plasma (15).

Schizophrenia and some other chronic psychotic disorders have inflammatory characteristics (16). Treatment with anti-inflammatory compounds appears to reduce the severity of some symptoms.

These observations, too, can be viewed as support for the concept of tertiary inflammatory damage. They go beyond, though, holding out the promise that systemic anti-inflammatory therapy might reduce the severity of symptoms of disorders with on-going inflammation. Because autism has some of the same inflammatory characteristics as schizophrenia (17), the possibility exists that systemic anti-inflammatory therapy might prove helpful here, too.

### ISSI and the Developing Brain—Animal Studies

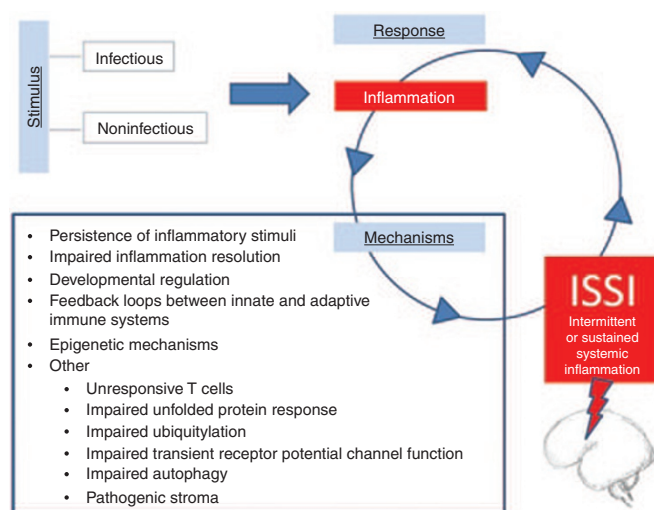
Thirty-five days after a local, apparently noninflammatory set of brain-damaging stimuli, immature rats’ microglia/macrophages, astroglia, and CD4 lymphocytes in the brain remained activated (18). Giving lipopolysaccharide, a powerful inflammatory stimulus, to pregnant rats is followed by apoptosis of brain cells in their newborn a week after birth (19). Three months following a hypoxic–ischemic insult to the brain of mouse pups, activated T lymphocytes were still present in the damaged hemisphere (20).

### ISSI and the Developing Brain—Human Studies

Elevated concentrations of inflammation-related proteins in the circulation on two separate occasions a week apart shortly after preterm birth provide information about an increased risk of microcephaly more than 2 y later (21). As mentioned above, school-aged children with cerebral palsy have higher TNF plasma levels than controls and their monocytes exhibit a more vigorous TNF response to lipopolysaccharide stimulation than monocytes from controls (15). In addition, the presence of astrocyte damage marker S100B in the systemic circulation of children with cerebral palsy suggests that the disease process might be ongoing/sustained as well (22). Elevated levels of inflammation-related proteins in blood collected on both postnatal days 7 and 14 are associated with impaired mental and motor development at age 2 y (23). ISSI also plays a prominent role in one framework proposed for the etiology of schizophrenia and autism (17).

## MECHANISMS

In this section, we try to answer the question, “What perpetuates inflammation to make it chronic?” (Figure 1). One possibility is that the inflammatory stimulus persists. A second is that the resolution of inflammation is hampered. Third, preterm newborns have developmentally regulated characteristics that allow reinforcement loops to sustain systemic inflammation (24). Fourth, positive feedback loops between innate and adaptive immune systems might perpetuate the inflammatory



**Figure 1.** Proposed list of candidate mechanisms linking infectious and noninfectious stimuli, the initial inflammatory response, and subsequent intermittent or sustained systemic inflammation (ISSI).

responses (25). A fifth candidate mechanism involves epigenetics. This section ends with a list of multiple miscellaneous but not mutually exclusive possibilities.

### Persistence of Inflammatory Stimuli

In the preterm newborn, assisted (i.e., mechanical) ventilation might be the most common prolonged/continued stimulus for systemic inflammation (26). One explanation for this link between assisted ventilation and systemic inflammation invokes barotrauma provocation of the local synthesis of inflammation-associated proteins, followed by translocation of some of these proteins from the lung to the circulation. In support of this interpretation is the observation that strategies that reduce ventilator-induced lung injury appear to reduce systemic inflammation in newborns (27). The presence of endotoxin in tracheal aspirates from mechanically ventilated newborns accompanied by inflammation-associated proteins suggests that some of the inflammation associated with assisted ventilation is the consequence of infection (28).

The other common systemic inflammation-provoking exposure among very preterm newborns is bacteremia (29,30). The reasons for their propensity to become bacteremic are complex, but include exposure to maternal organisms, need for assisted ventilation, fragile skin, impaired T(H)17-polarizing cytokine production, and deficient expression of complement, as well as a deficiency of antimicrobial proteins and peptides (31). The acquisition of gut microbiota at the time the intestinal epithelium is immature might contribute to the translocation of bacteria from the gut to the adjacent blood vessels and their blood contents (32).

Toll-like receptors (TLRs) are pattern recognition receptors that can recognize pathogen-associated molecular patterns (including bacterial components), as well as endogenous substances released during/following injury and inflammation (including oxidized phospholipids, oxidized low-density

lipoproteins,  $\beta$ -defensin, high-mobility group protein 1, and heat shock proteins) (33). When these activate TLR-2 or TLR-4, the result is induction of the transcription factor nuclear factor- $\kappa$ B, which then promotes the synthesis and release of such inflammation-related proteins as interleukin (IL)-6 and TNF- $\alpha$ . The resulting inflammation and injury can thereby promote chronic inflammation.

## Inflammation Resolution

The normal inflammatory response includes components that contribute to the termination of the inflammatory response (34). This resolution of inflammation is tightly regulated by anti-inflammatory proteins, such as IL-4, IL-5, IL-10, and IL-13 (35) and proresolving proteins, especially transforming growth factor- $\beta$  (36). Preterm newborns appear to have a paucity of some of these proteins (37,38).

Other endogenous products of inflammation contribute to resolution. Among these are a variety of lipid mediators derived from arachidonic acid in the plasma membrane, including prostaglandins, lipoxins, and resolvins. We still do not know how capable the preterm newborn is in synthesizing these lipid-based inflammation-resolution promoters.

A subset of neutrophils from preterm newborns when exposed to inflammatory stimuli appears to be relatively resistant to apoptosis (39). The continued presence of such cells in term newborns (40) can contribute to continued (i.e., subacute and/or chronic) inflammation. Indeed, the pool of such apoptosis-resistant cells appears to be relatively larger in newborns than adults (41). Here, too, we do not know how much the prolonged presence of these apoptotic-resistant cells enhances the probability of ISSI.

## Developmental Regulation

Data from observational and experimental studies document that, once initiated, the fetal/neonatal inflammatory response can be sustained for long intervals (4). Phenomena that vary with gestational age are identified as “developmentally regulated.” Several components of the inflammatory response of preterm newborns that are deemed “developmentally regulated” might account for some of the inflammatory hyperresponsiveness and persistence that has been documented.

Following an intravenous inflammatory stimulus (i.e., lipopolysaccharide), healthy young adults volunteers have TNF- $\alpha$  and IL-6 concentrations that peak at about 2 to 2½ hours and return to baseline within 12 h (42). In preterm newborns, however, some indicators of systemic inflammation (proinflammatory cytokines) are elevated after birth much longer than would be expected based on their half-life in adults (43,44). We still do not know the half-life of inflammation-related proteins in preterm newborns. Consequently, we do not yet know if the sustained inflammation reflects nothing more than a developmentally regulated very prolonged catabolic process.

Compared to their counterparts at term, preterm rats and humans appear to have limited ability to synthesize proteins with anti-inflammatory characteristics (45,46). Despite this weak anti-inflammatory capability, very preterm newborns

appear to be capable of a more vigorous systemic inflammatory response than gestationally older newborns (47,48). The result is a propensity to a proinflammatory imbalance of proteins that is not readily eliminated.

## Positive Feedback Loops Between Innate and Adaptive Immune Systems

In adults, the innate and adaptive immune systems reinforce each other (49). Support has been provided for the possibility that the innate and adaptive immune systems reinforce each other in the very preterm newborn, thereby prolonging the inflammation and increasing the likelihood of brain damage (25). Part of this phenomenon might be due to an insufficient number of T cells that leads to “uncontrolled” inflammation (50). In addition, proinflammatory cytokines and other aspects of the inflammatory environment have the potential to diminish the response of effector T cells to regulation (51).

## Epigenetic Mechanisms

Epigenetic processes modify gene expression and/or cell phenotype without altering the genomic DNA (11). Many of these pack/unpack (i.e., tighten/loosen the bonds of) chromatin. For a gene to be transcribed, it has to be “unpacked” from the chromatin (52). In turn, a gene can be silenced by “packing” the chromatin. The two mechanisms most often involved in transforming the chromatin alter nucleosomal histones, or micro(noncoding)-RNA expression. DNA methylation is another epigenetic mechanism.

Normal acute systemic inflammation follows a set pattern beginning with an initiation (proinflammatory) phase, rapidly followed by an adaptive (anti-inflammatory) phase, and finally a resolution (restoration of homeostasis) phase (7). These phase shifts are accompanied by changes in gene expression, some due in part to epigenetic processes. The shift from a proinflammatory to an anti-inflammatory state, for example, is accompanied by the repression of some genes and the activation of others (53).

Inflammation-stimulated cells undergo extensive transcriptional reprogramming mediated, in part, by inducing histone deacetylases (54) and by enhancing methylation and/or acetylation at specific histone proteins (55).

Just as chromatin reorganization (including histone deacetylation) contributes to inflammation opening access to promoters of acute proinflammatory genes, subsequent chromatin reorganization (including histone acetylation), tends to close access to these promoters of acute proinflammatory genes, thereby facilitating the transition to the anti-inflammatory state (56). Some histone deacetylases, however, put a brake on the propensity to resolve inflammation (57), while other histone deacetylases appear to promote inflammatory gene expression in response to inflammatory stimuli (58). The net effect of histone deacetylation, however, is inflammation promotion (59).

Some micro-RNA influence inflammation, and inflammation, in turn, influences the biogenesis of some of these, as well as other micro-RNAs (60). Some of these micro-RNAs

dampen the inflammatory process, while others potentiate the immune response.

#### Miscellaneous Additional Mechanisms

Ongoing tissue destruction leads to continued inflammation. Necrosis of any cells, including brain cells, leads to the release of cellular proteins and other nuclear/cell contents. Some of these function as damage-associated molecular patterns that, once outside the cell, can induce noninfection-associated immune responses (61). The result is continued inflammation. Some of the damage-associated molecular patterns generated during traumatic injury leak into the systemic circulation (62). If the damage-associated molecular patterns released by brain damage within the blood–brain barrier of preterm newborns leak into the systemic circulation and contribute to ISSI, might the developing brain be less able than the mature brain to contain damage-associated molecular patterns within the blood–brain barrier?

Inflammatory phenomena induce endoplasmic reticulum stress, which, in turn, leads to the unfolded protein response, which is followed by even more inflammation (63). The relationship between the ubiquitin proteasome system and inflammation is complex (64). Normally, the induction of proteasomes clears accumulating misfolded proteins, thereby minimizing continued inflammation. Consequently, impairments of ubiquitylation can contribute to continuing inflammation. Products of inflammation acting on transient receptor potential channels can promote the release of substances that promote further inflammation (65). Autophagy is an intracellular mechanism that removes damaged or unused cell components, including inflammatory stimuli (66). Because impairments of autophagy allow some of these to remain, they allow the inflammation to continue. Finally, stroma includes fibroblasts, as well as blood and lymphatic vessels. “The stroma, formerly considered the theatrical stage of the inflammatory process, has acquired, in recent years the role of director of the immune response, regulating the process of leukocyte recruitment, organization of leukocytes within the tissue and exit via the escape route of the lymphatic endothelium” (67). Continued inflammation can result in the acquisition by stromal cells of novel features that can contribute to the perpetuation of inflammation.

#### Intervention Design

Multiple potential anti-inflammatory and/or immunomodulatory intervention schemes are conceivable with the perinatal brain in mind (68,69). If ISSI indeed contributes to brain damage in the preterm newborn over an extended time period, a wide window of opportunity would open for such intervention (4), perhaps even after the onset of the initiator of ISSI. Targeting the mechanisms of ISSI discussed above seems to be a reasonable strategy when thinking about future interventions to curb its adverse effects.

#### CONCLUSION

Intermittent or sustained inflammation appears to characterize a large number of disorders of different organs. Here, we focus on the newborn brain, especially the brain of infants

born months before term, and offer evidence that the very preterm newborn has the capacity to sustain inflammation, thereby increasing the risk of brain damage.

#### STATEMENT OF FINANCIAL SUPPORT

The authors received funding from the National Institute of Neurological Disorders and Stroke, National Institutes of Health (NIH, Bethesda, MD; grants 5U01NS040069-05; 2R01NS040069-06A2), the National Eye Institute (NIH; grant 1-R01-EY021820-01A1), and the National Institute of Child Health and Human Development (NIH; grant 5P30HD018655-28).

Disclosure: The authors have no financial ties to disclose.

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