Long-term pathological consequences of prenatal infection: beyond brain disorders

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Labouesse MA, Langhans W, Meyer U. Long-term pathological consequences of prenatal infection: beyond brain disorders. Am J Physiol Regul Integr Comp Physiol 309: R1–R12, 2015. First published April 29, 2015; doi:10.1152/ajpregu.00087.2015.—Prenatal immunological adversities such as maternal infection have been widely acknowledged to contribute to an increased risk of neurodevelopmental brain disorders. In recent years, epidemiological and experimental evidence has accumulated to suggest that prenatal exposure to immune challenges can also negatively affect various physiological and metabolic functions beyond those typically associated with primary defects in CNS development. These peripheral changes include excessive accumulation of adipose tissue and increased body weight, impaired glycemic regulation and insulin resistance, altered myeloid lineage development, increased gut permeability, hyperpurinemia, and changes in microbiota composition. Experimental work in animal models further suggests that at least some of these peripheral abnormalities could directly contribute to CNS dysfunctions, so that normalization of peripheral pathologies could lead to an amelioration of behavioral deficits. Hence, seemingly unrelated central and peripheral effects of prenatal infection could represent interrelated pathological entities that emerge in response to a common developmental stressor. Targeting peripheral abnormalities may thus represent a valuable strategy to improve the wide spectrum of behavioral abnormalities that can emerge in subjects with prenatal infection histories.

Prenatal exposure to infectious pathogens or inflammatory stimuli is increasingly recognized to play an important etiological role in neuropsychiatric and neurological disorders with neurodevelopmental components (15, 21, 93, 99, 100). Significant associations between prenatal infection during pregnancy and increased disease risk in later life have been revealed for various brain disorders, including schizophrenia (19), autism (7, 117), bipolar disorder (22, 116), mental retardation (61), and cerebral palsy (31, 50). Hence, prenatal exposure to immune challenges may be best viewed as a general vulnerability factor for neurodevelopmental brain disorders rather than a disease-specific risk factor (52, 100). In this sense, the adverse effects induced by prenatal infection may reflect an early entry into a deviant neurodevelopmental route, but the specificity of subsequent disease or symptoms is likely to be influenced by the genetic and environmental context in which the prenatal infectious process occurs. This concept would, indeed, be consistent with the emerging evidence suggesting that seemingly remote disorders, such as schizophrenia, autism, attention-deficit/hyperactivity disorder, and major depression share considerable amounts of risk factors and brain dysfunctions (23, 92, 138). The presence of shared genetic and environmental risks among those illnesses has led to the proposal that they might lie along a continuum of genetically and environmentally induced neurodevelopmental causalities (103, 113), wherein prenatal infection may be one of the many factors that shape the eventual pathological outcomes.

While the importance of prenatal immunological adversities has been widely acknowledged in the fields of developmental neuropsychiatry and neurology, less attention has been paid to the possibility that prenatal exposure to infection may also play an etiological role beyond central nervous system (CNS) disorders. Hence, the possible long-term effects of prenatal infection on disorders that are not primarily associated with CNS dysfunctions may be somewhat underestimated. This seems surprising for various reasons. The prenatal period is not only a highly sensitive period for early brain development (99), but also for other biological systems that develop in utero, including the innate and adaptive immune systems (47, 70), the cardiovascular system (46, 60), the renal system (55, 80), adipose tissue (140), and skeletal bones and muscles (20, 68). It is, in fact, rather unlikely that maternal infection during pregnancy would specifically disrupt fetal brain development; instead, it may more generally represent a developmental stressor for the entire organism. The underlying assumption for this hypothesis is that infection leads to the secretion and circulation of various immune system-related factors in the maternal host and fetal environment, which, in turn, are likely...
to affect peripheral organs and brain structures in the developing organism to the same extent.

Another reason why we should not ignore CNS-remote effects of prenatal infection relates to the clinical observations that individuals with major psychiatric disorders often display signs of physiological and metabolic dysfunctions, including insulin resistance, Type 2 diabetes, obesity, and cardiovascular disease (90). Even though chronic psychopharmacotherapy may facilitate or even induce such abnormalities (40, 139), it is becoming increasingly evident that they cannot solely be accounted for by chronic drug exposure. Indeed, certain metabolic and physiological dysfunctions often occur (albeit in a somewhat less severe form) in drug-naïve or minimally medicated first-episode patients with mental illnesses (63, 124, 143, 153). These findings have been taken as circumstantial evidence that at least some of the metabolic and pathophysiological comorbidities in major brain disorders may have a developmental origin and, thus, emerge prior to the onset of full-blown psychiatric illness.

Finally, neurodevelopmentally acquired brain abnormalities in response to maternal infection may also facilitate the development of metabolic and physiological dysfunctions across the postnatal life span. For example, the development of homeostatic brain regions, such as the hypothalamus, encompasses a number of steps that begin early in fetal life and continue postnatally (135). Infection-induced maldevelopment of such brain regions could thus impair the homeostatic control of various physiological functions, including food intake, renal functions, and reproduction (81, 89).

Here, we review the existing evidence indicating that the long-term pathological consequences of prenatal immune challenges are not solely confined to primary CNS disorders. Instead, they extend more globally to other physiological and metabolic dysfunctions in peripheral systems. Relevant studies were identified and selected using PubMed. All articles published before December 2014 were screened for relevance and were searched using the following search criteria (in alphabetical order) in various combinations: “animal model,” “autism,” “bipolar disorder,” “body weight,” “cytokines,” “diabetes,” “dopamine,” “epidemiology,” “food intake,” “glucose,” “gut,” “homeostasis,” “hypothalamus,” “immune activation,” “infection,” “inflammation,” “LPS,” “maternal,” “metabolism,” “metabolic syndrome,” “microbiota,” “microglia,” “obesity,” “polyI(C),” “pregnancy,” “prenatal,” and “schizophrenia”. In addition to reviewing the available literature, we also provide a conceptual framework suggesting that several apparently unrelated central and peripheral effects of prenatal infection may not represent separate pathological entities but could, in fact, result from interrelated pathological mechanisms that are engaged in response to a common developmental stressor.

**Obesity and Metabolic Dysfunctions**

Epidemiological investigations in humans and experimental work in animals both emphasize a critical role of the early-life environment in shaping postnatal metabolic functions. Stimulated by the seminal work of David Barker and colleagues, the concept of “early-life priming of adult disease” is now widely accepted for various adverse health outcomes (37). In the context of obesity and metabolic disorders, this concept refers to the phenomenon that exposure to a specific environmental factor during early prenatal or perinatal periods can induce lifelong changes in metabolic functions, thereby predisposing the organism to excessive adiposity and associated pathophysiological conditions, including impaired glucose homeostasis, insulin resistance, Type 2 diabetes, and cardiovascular disease (81, 89).

One of the most noticeable early-life adversities precipitating such metabolic dysfunctions is maternal obesity during pregnancy (54, 141). Indeed, a robust association between prenatal maternal obesity and an enhanced risk for metabolic disorder in the offspring has been established by a plethora of human epidemiological studies and translational animal models (41, 77). Because obesity is accompanied by chronic low-grade inflammation (105, 131), it has been suggested that enhanced systemic and placental inflammation in obese mothers may represent one of the mediating factors underlying the developmental disruption of metabolic functions in the offspring (121, 127). Only relatively recently, however, epidemiologists have begun to explore more directly whether discrete maternal exposure to infectious or inflammatory stimuli is similarly associated with increased risk for metabolic disorder in the offspring. A first line of evidence supporting this hypothesis comes from a human epidemiological study that used a cross-sectional cohort design, in which more than 17,000 male singletons were included (25). The findings from this study suggested a 34% increased risk of obesity [defined on the basis of a body mass index (BMI) of 30 kg/m² or more] after being born to a mother with infection during pregnancy (25). Interestingly, a similar positive association has also been found following childhood infections (25), suggesting that the developmental period for infection-induced changes in adiposity extends to the early postnatal life.

Work in developmental rodent models further supports the hypothesis of causal effects between maternal immune challenge during pregnancy and long-term metabolic dysfunctions in the offspring. For example, it has been shown that maternal treatment with the bacterial endotoxin LPS during mid-pregnancy in rats induces a wide spectrum of metabolic disturbances in the adult offspring, including increases in body weight and adipose tissue, hyperphagia, and insulin resistance (111). These effects were sex-specific and emerged in male but not female rats, indicating that male offspring are more vulnerable than females in terms of developing metabolic abnormalities following maternal endotoxemia during pregnancy. Findings from other rodent models of maternal immune activation further suggest that the association between prenatal immune challenge during pregnancy and development of metabolic disturbances is not dependent on the precise identity of the infectious or inflammatory pathogen. In fact, such metabolic effects can even be induced by prenatal exposure to specific inflammatory cytokines (29). Moreover, long-term metabolic abnormalities have also been observed in mouse offspring of mothers that were exposed to the viral mimetic polyribonucleosinic-polyribocytidilic acid (polyI:C), a synthetic analog of double-stranded RNA that induces a virus-like acute phase response (93). In this virus-like immune activation model, offspring of polyI:C-treated mouse dams were shown to develop altered glycemic regulation and abnormal...
ingestive behavior in adolescence and excess fat deposition in adulthood (115). Similar results were obtained in a mouse model, in which pregnant mice were infected with Ljungan virus (LV), a virus that belongs to the Picornavirus family and is virulent for laboratory rodents (126). Maternal LV exposure in mice has been shown to predispose the offspring to signs of Type 2 diabetes and obesity (110). These effects, however, were particularly manifest in LV-exposed mice that experienced additional stress during adolescence, suggesting that the severity of metabolic abnormalities following prenatal immune activation can be exacerbated by exposure to other environmental adversities, such as adolescent stress (110). These findings are particularly relevant for the multifactorial etiology of obesity and Type 2 diabetes, which are likely caused by a combination of environmental (and genetic) factors (38, 81).

Peripheral (and Central) Inflammation

Various rodent models demonstrate that maternal exposure to infectious or immune system-activating agents leads to robust post-acute immune changes at the maternal-fetal interface, including the placenta, amniotic fluid, and fetal organism (2, 6, 96, 97, 151, 154). The nature and/or severity of these changes are influenced by various factors, most notably the identity and/or intensity of the pathogen (51, 94), the gestational timing of exposure (97), and the genetic background of the infected host (2, 96, 154). Despite this, it seems that maternal exposure to distinct infectious or immune system-activating agents leads to partially overlapping immune responses in the fetal system. These overlapping effects are mostly characterized by increased fetal expression of inflammatory factors, such as proinflammatory cytokines and chemokines (5). It is believed that abnormal expression of inflammatory factors in the fetal brain contribute to, or even mediate, abnormal brain and behavioral development following prenatal exposure to infection (79, 136). Indeed, as reviewed extensively elsewhere (95, 102), acute inflammation during early fetal brain development may negatively affect ongoing neurodevelopmental processes, such as neuronal/glial cell differentiation, proliferation, migration, and survival, and, thus, predispose the developing offspring to long-term brain and behavioral dysfunctions.

Since signs of subchronic systemic (and central) inflammation are often present in at least a subset of patients with neurodevelopmental disorders (64, 86, 92, 101, 150), considerable research has been undertaken to address the question of whether maternal exposure to infectious or inflammatory agents may lead to persistent inflammatory changes in the offspring postnatally. The evidence for this hypothesis is, at best, equivocal. Some studies using rodent models of bacterial or viral maternal immune challenge have reported a significant upregulation of circulating inflammatory factors such as proinflammatory cytokines or chemokines in the juvenile or adult offspring (17, 43, 69). Other studies using the same animal models, however, failed to find clear signs of systemic inflammation in juvenile or adult offspring born to immunologically challenged mothers (96, 157), or they even reported opposite effects that were characterized by blunted systemic inflammatory activity following prenatal infection (115).

Inconclusive data also exist with respect to central inflammation. In the CNS, microglia and astrocytes are the major immunocompetent cells, which drive both the induction and limitation of inflammatory processes (122). This is achieved through the synthesis of proinflammatory and anti-inflammatory cytokines, upregulation, or downregulation of various cell surface receptors, such as pathogen recognition receptors, cytokine receptors, and numerous receptors crucial for antigen presentation. Enhanced microglia activation in brain parenchyma, along with increased central production of secreted inflammatory factors, is often taken as a sign of ongoing inflammation in the CNS (48). The possibility that prenatal infection leads to chronic signs of brain inflammation has been supported only by some studies in rats and mice (17, 69), whereas other rodent studies failed to find evidence for such neuroinflammatory processes extending into neonatal or adult life (5, 43, 96, 119, 151, 157).

The inconsistency surrounding the long-term effects of prenatal infection on the persistence of inflammatory processes across the postnatal life span may be explained by various factors, most notably the severity and/or chronicity of the infectious process targeting the maternal host. Indeed, it appears that more marked postnatal inflammatory changes are seen following relatively severe forms of maternal immune challenge, such as chronic exposure to immune system-activating agents throughout the entire gestational period (17). In contrast, acute or subchronic prenatal exposure to immune system-activating stimuli in mice and rats appears to be largely devoid of systemic and central inflammatory effects persisting into the juvenile or adult period (5, 43, 96, 119, 151, 157). The latter may not seem surprising because inflammation is typically counteracted by homeostatic processes that mount anti-inflammatory and/or immunosuppressive responses upon the induction of inflammation (132), which, in turn, dampen and finally resolve the post-acute fetal inflammatory responses to maternal immune activation (91).

Still, the developing organism might sustain latent inflammatory abnormalities that may not become apparent until reappearance to specific immunogens postnatally. In support of this hypothesis, it has been shown that prenatal virus-like immune activation in mice leads to a persistent decrease in the number of regulatory T cells (Treg) in the spleen and mesenteric lymph nodes (58). Besides other functions, Treg can potentely suppress innate and adaptive immune responses, so that a disruption of normal Treg functions can lead to exacerbated inflammatory reactions (24). Such an exacerbation is seen in mouse offspring born to immunologically challenged mothers, which mount a potentiated proinflammatory T-cell response to immunogenic T-cell stimulation (58).

Prenatal virus-like immune activation in mice has further been shown to induce long-term changes in macrophage function that persist into adulthood. More specifically, bone marrow-derived macrophages of prenatally poly(I:C)-exposed mice show an augmented proinflammatory cytokine response to in vitro LPS stimulation alone, or in combination with interferon (IFN)-γ (112). The costimulation with LPS and IL-4 does not result in a similar proinflammatory cytokine signature (112). Collectively, these results indicate that prenatal virus-like immune activation potentiates the polarization of macrophages toward an M1 phenotype, which, in turn, is typically associated with larger production of proinflammatory cytokines, such as IL-12, at the expense of reduced production of anti-inflammatory cytokines, such as IL-10 (85, 106). Thus, it
seems that prenatal immune activation can prime the offspring’s peripheral immune system in such a way that it mounts more excessive proinflammatory responses in the event of postnatal pathogen (re-)exposures.

It should also be pointed out that prenatal immune activation can similarly lead to latent immune abnormalities in the CNS. As reviewed in detail elsewhere (14, 50), numerous experimental studies in rodents show that immunological exposure in early (prenatal or neonatal) life can cause the organism to mount differential (and often more vigorous) CNS inflammatory responses to subsequent immunological or nonimmunological challenges. For example, even though prenatal virus-like immune activation per se does not cause overt glial abnormalities and associated inflammatory changes in the brain parenchyma of mouse offspring (5, 43, 157), signs of microglia overactivation and exacerbated inflammatory cytokine secretion in CNS areas can be induced in these offspring when they are additionally exposed to subchronic stress postnatally (44). This form of immune sensitization or priming suggests that prenatal immune activation can markedly increase the vulnerability of the offspring to brain immune changes in response to stress. A similar microglia-priming effect by prenatal immune challenge has been demonstrated in a virus-like immune activation model, in which mouse offspring were subjected to either prenatal poly(I:C) treatment alone, or in combination with a second poly(I:C) treatment regimen in late adulthood (69). In this model, mice exposed to both prenatal and postnatal poly(I:C) treatment showed more extensive microglia activation and astrogliosis compared with either treatment alone (69).

Taken together, even though the long-term effects of prenatal immune activation on peripheral and central inflammatory responses may not be apparent under basal conditions, they may become so when the offspring are exposed to additional environmental challenges, such as stress or acute infection during the postnatal life. In addition, persistent inflammatory abnormalities may develop more locally and may thus emerge in specific peripheral organs. The latter possibility is discussed in more detail in the subsequent section.

**Gastrointestinal Abnormalities and Dysbiosis**

In recent years, there has been an increasing interest in the relative potential of gastrointestinal (GI) functions to modulate neuropsychological traits implicated in psychiatric disorders (28, 87, 88). Epidemiological and clinical studies have repeatedly demonstrated a high comorbidity between GI inflammatory disorders and stress-related psychiatric symptoms, such as anxiety or depressive behavior (28, 36). These findings have been complemented by experimental studies in rodents showing that abnormal development of the gut microbiota leads to neuroendocrine, neurochemical, and emotional abnormalities, some of which are reminiscent of hormonal and behavioral aberrations typically seen in depression and/or anxiety disorders. For example, ablation of the commensal GI microbiota in germ-free mice or by chronic antimicrobial compounds can lead to functional changes in the hypothalamus-pituitary-adrenal (HPA) axis and in the central dopaminergic, serotonergic, and GABAergic neurotransmitter systems, and these effects are further linked to the emergence of increased anxiety-like behavior (11, 35).

Other clinical populations, for which GI abnormalities and dysbiosis seem clinically relevant, comprise individuals suffering from neurodevelopmental psychiatric illnesses. Indeed, in addition to the pathological symptoms traditionally attributed to CNS dysfunctions, neurodevelopmental psychiatric illnesses, such as autism and schizophrenia, are also associated with a number of GI dysfunctions. Such abnormalities include chronic intestinal low-grade inflammation, increased intestinal permeability (“leaky gut”), allergic reactions to dietary proteins, diarrhea, gastric dysmotility, and alterations in gut microbiota (16, 26, 133, 136). By further undermining general physical health and daily life quality, GI distress induces an additional clinical burden to patients suffering from psychiatric disorders (9, 53).

In view of the etiological contribution of prenatal infection to neurodevelopmental diseases, experimental research has begun to explore whether early-life immune challenges may be a relevant environmental risk factor for the development of GI abnormalities. In a seminal recent study, Hsiao et al. (58) demonstrated that prenatal polyI:C-induced immune activation in mice can indeed cause long-term defects in intestinal integrity and alterations in the composition of the commensal microbiota. The former effect was evident by increased translocation of dextran across the intestinal epithelium and was associated with decreased colonic expression of tight junction components. Interestingly, signs of intestinal disintegrity in polyI:C-exposed mouse offspring were already present by the age of 3 wk, suggesting that these abnormalities are established during early life. Furthermore, the colons from prenatally infected mice displayed increased expression of the inflammatory cytokine IL-6, which is in line with the notion that increased gut permeability is commonly associated with altered immune responses in the GI tract (148). Offspring of immunologically exposed mouse dams also markedly differed from control offspring in terms of their gut microbiota composition, and this difference was mostly accounted for by differences in the relative abundance of Clostridia and Bacteroidia classes (58).

The study by Hsiao et al. (58), which used a mouse model of virus-like immune activation, is, thus far, the only one that directly assessed the influence of prenatal immune challenge on the development of GI abnormalities in the offspring. Hence, it remains essentially unknown whether similar effects can also be induced by prenatal exposure to other infectious or inflammatory agents. It should be noted, however, that remarkable changes in the gut microbiota composition and associated intestinal abnormalities have also been identified in another experimental model of neurodevelopmental disease, namely prenatal exposure to valproic acid (VPA) in mice (34). Similar to the polyI:C model (83), the VPA model is frequently used to induce autism-related brain and behavioral abnormalities in experimental rodents (123). Thus, it appears that prenatal exposure to distinct environmental factors does not only induce overlapping neurobehavioral phenotypes, but further induce similar changes in GI functions and microbiota. It remains currently unknown whether the latter commonalities may be explained by mutual pathogenic mechanisms, whereby neurodevelopmentally acquired abnormalities could increase the vulnerability to GI pathology through mechanisms involving a
disruption of the normal top-down (CNS to GI tract) signaling. This possibility is discussed in more detail below.

Do Peripheral Abnormalities Contribute to Neurobehavioral Deficits Following Prenatal Infection?

Even though the evidence for altered peripheral functions in prenatally infected subjects is emerging, it remains largely elusive whether these abnormalities functionally contribute to the manifestation of neurobehavioral deficits. In other words, do peripheral and central abnormalities, which can both be precipitated by early-life adversities such as prenatal infection, represent separate pathological entities? Or is there a pathological connection between the two, so that functional abnormalities in the former can lead to pathological changes in the latter?

It is obvious that the latter scenario would require bottom-up (periphery to CNS) and top-down (CNS to periphery) pathways that allow a bidirectional communication between the brain and the peripheral systems. As extensively reviewed elsewhere (12, 27, 28, 88), such pathways, indeed, exist and are evolutionarily well conserved across species. In fact, this bidirectional communication between the CNS and periphery is pivotal for body homeostasis and adaptive responses to changes in environmental conditions. Various peripheral signals such as GI peptides, cytokines, neuroactive bacterial metabolites, and adipose-derived factors can be relayed to the CNS via multiple routes, including the vagal afferents and the blood circulation (12, 27, 28, 88). The latter allows transport of systemic signals into the CNS through specialized transport systems embedded in the blood-brain barrier (BBB), or at sites lacking a complete BBB, such as the circumventricular organs. Afferent vagal nerve fibers are the main neuronal pathways through which peripheral signals can be conveyed to the brain (Fig. 1). Vagal afferent neurons synapse bilaterally on the nucleus tractus solitarii, from where neuronal signals are transmitted to other brain stem nuclei and to various forebrain structures, such as the hypothalamus, nucleus accumbens, amygdala, and prefrontal cortex (12). On the other hand, the periphery is connected with and modulated by the CNS through neuronal efferent branches of the sympathetic and parasympathetic nervous systems, which regulate visceral functions, both at rest and in response to activating stimuli (134). The periphery is further regulated by factors secreted by various neuroendocrine systems, such as the HPA axis, which has a central role in regulating many homeostatic processes, particularly in response to stress-related stimuli (10).

In view of these elaborated bidirectional communication pathways, it may not be surprising that interventions directed at peripheral targets have the potential to ameliorate neurobehavioral deficits in offspring exposed to prenatal infection. A proof of concept for this notion has recently been realized using oral antipurinergic therapy using acute administration of suramin (58). On the basis of their subsequent findings showing that prenatal virus-like immune challenge in mice leads to impaired GI functions and dysbiosis, Hsiao et al. (59) went on to show that oral treatment with the human commensal _Bacteroides fragilis_ normalizes gut permeability and microbial composition and further corrects autism-related behavioral deficits in mouse offspring born to immunologically challenged mothers. Together, these findings support the hypothesis that gut- and immune system-related peripheral abnormalities following prenatal infection have a direct impact on CNS functions, so that normalization of the former leads to beneficial effects on the latter.

A similar conclusion can be drawn from a recent investigation in mice demonstrating a link between prenatal virus-like immune activation and the emergence of altered purine metabolism in plasma (108). Besides other metabolic changes, offspring of immunologically challenged mouse dams showed marked signs of hyperpurinergia, a pathophysiological condition that is characterized by increased (plasma) levels of purines. Importantly, Naviaux et al. (108) showed that an antipurinergic therapy using acute administration of suramin not only normalizes the peripheral metabolic abnormalities in prenatally infected mice, but further corrects several of the behavioral deficits typically observed in untreated offspring. In
addition to immunological and gut-related factors (58, 59), alterations in blood purine metabolism, thus, seem to be another peripheral pathology that readily contributes to the emergence of behavioral deficits following prenatal infection (108).

Thus far, it remains unknown whether other metabolic disturbances that are induced by prenatal infection, including alterations in glycemic regulation, insulin insensitivity, and increased adiposity, may also directly influence behavioral functions in subjects with a history of prenatal infection. Hence, it remains to be determined whether normalization of these metabolic abnormalities may exert beneficial effects on behavioral deficits in this population. Furthermore, the precise link between individual peripheral abnormalities also remains elusive. For example, it is not known whether the excessive accumulation of adipose tissue in offspring of infected mothers may facilitate excessive proinflammatory signaling. Such a link has been demonstrated in various models of obesity, but it still awaits direct verification in models of prenatal immune challenge. Given the emerging functional relationships between the gut microbiome and obesity and between the gut microbiome and Type 2 diabetes (144), it would also seem warranted to explore such possible connections in the context of pathologies that are associated with prenatal exposure to infection.

Do Neurodevelopmental Deficits Contribute to Peripheral Abnormalities Following Prenatal Infection?

While a direct influence of peripheral abnormalities to CNS dysfunctions is supported by at least some animal studies, it remains essentially unknown whether the opposite scenario holds true as well. Hence, the role of neurodevelopmentally acquired CNS dysfunctions in promoting peripheral abnormalities following prenatal infection still awaits thorough examination. In view of the elaborated top-down (CNS to periphery) communication pathways (Fig. 1), however, it seems feasible that abnormal functioning of discrete neuronal and neuroendocrine systems can, at least to some extent, facilitate the development and/or maintenance of peripheral abnormalities.

Perhaps one of the most obvious examples in this context relates to the crucial role of the hypothalamus and interconnected structures in controlling food intake and energy balance (104, 129). Given that maternal immune activation alters hypothalamic functions in rodent offspring (42, 78, 158), neurodevelopmentally acquired abnormalities in the hypothalamus may contribute to the emergence of a hyperphagic phenotype in offspring with prenatal infection (111, 115). An alternative (but not mutually exclusive) mechanism underlying such changes in food intake may be related to changes in the mesocorticolimbic dopamine system. A plethora of investigations support a key role of dopamine in reward and incentive values on the one hand, and in the associations between reward and eating behavior on the other hand. These functional associations are highly complex and likely involve intricate interactions among homeostatic, hedonic, motivational, and associative processes (62, 104, 125). Prenatal immune activation in rats and mice is well known to induce primary defects in early dopaminergic development (91, 155) and to lead to long-term dopaminergic abnormalities in the adult offspring (4, 98, 114, 155, 160). It seems, therefore, plausible that such dopaminergic dysfunctions may be involved in the development of altered food intake and energy balance, be it because of changes in homeostatic, hedonic, motivational, and/or associative processes.

Another possible association that warrants careful examination in future studies is the potential impact of altered autonomic nervous system (ANS) functions in prenatally infected animals. Initial evidence suggests that prenatal immune activation can cause hyperactivity of the sympathetic nervous system, perhaps at the expense of diminished parasympathetic nervous system functions. Hyperactivity of the sympathetic nervous system typically leads to increased secretion of noradrenaline and corticosterone, both of which have been observed in mouse offspring that were exposed to prenatal immune challenge (115, 158). Prolonged secretion of these stress-related factors can negatively influence GI physiology, including gut motility, secretion, permeability, and composition of the gut microbiota (13, 67). Given that some of these GI abnormalities have been shown to develop in mice exposed to prenatal immune challenge (59), it would appear highly warranted to explore whether they may be causally related to a hyperactivity of the sympathetic nervous system.

At the same time, diminished activity of the parasympathetic branch of the ANS may contribute to the development of altered inflammatory responses in the GI tract and other peripheral organs (120). Indeed, efferent vagal pathways originating from the dorsal motor nucleus of the vagus possess anti-inflammatory activity by releasing ACh, which, in turn, inhibits proinflammatory cytokine secretion by peripheral immune cells upon binding to α7 nicotinic receptors (118, 145). This parasympathetic mechanism of neuronal anti-inflammatory signaling has been termed “the cholinergic anti-inflammatory pathway” and seems to play an important role in dampening peripheral inflammatory responses (118, 145). Whether this pathway is altered by prenatal exposure to infection still awaits direct examination, but it could provide a contributing factor for the prenatal infection-induced disturbances in local inflammatory responses, including intestinal inflammation (59).

Possible Mechanisms Mediating the Effects of Maternal Infection on the Offspring

The precise mechanisms responsible for mediating the pathological effects of maternal infection on the developing organism in utero remain to be determined. In fact, several plausible mechanisms exist, whereby maternal infection can negatively affect the normal development of peripheral (and central) organs. As summarized in Fig. 2, the different pathological mechanisms induced by infection may not be mutually exclusive, but may rather interact with each other to affect various developmental processes that take place in prenatal life.

One prevalent hypothesis suggests that common immunological factors, in general, and inflammatory cytokines, in particular, are key mediating factors changing developmental trajectories in the offspring (4, 45, 79, 96, 102, 137). Inflammatory cytokines are typically induced during the acute phase response to infection (146, 147) and may represent a major developmental stressor for the organism (18, 57, 95). In the event of maternal infection, an increase in fetal cytokine levels may be caused by placental transfer of maternally pro-
The hypothalamus and of adrenocorticotropic hormone from the stimulating the release of corticotropin-releasing factor from reactions further lead to the activation of the HPA axis by infection and the subsequent cytokine-associated inflammatory development trajectories in the offspring (74, 75).

Models suggest that infection-induced increases in fetal ROS and reactive oxygen species, and soluble endocrine factors, such as stress hormones. Some of these factors might cross the placental barrier and enter the fetal environment, thereby causing fetal inflammation and oxidative stress. Abnormal fetal expression of these factors might impair the normal development of peripheral and central organs by modifying the differentiation, proliferation, and/or migration of target cells. These processes may involve alterations in gene expression via epigenetic modifications. Maternal infection during pregnancy can further induce inflammatory response in the placenta and cause placental insufficiency, which, in turn can cause fetal hypoxia. In addition, infection can cause (temporary) states of macronutrient and micronutrient deficiency, which limit the fetal availability of essential nutrients necessary for normal fetal development and growth. Finally, maternal infection during pregnancy can modify the microbial composition of the placenta, which might alter the development of the offspring’s microbiome and thus predispose the developing organism to dysbiosis and other microbiome-associated abnormalities.

Reduced cytokines (30, 159), by placental production of cytokines (6, 56, 128), or by increased fetal cytokine synthesis (97). In addition to its effects on inflammatory cytokine secretion, infection and the subsequent induction of inflammatory responses are also strongly associated with numerous other pathophysiological effects, including oxidative stress. Oxidative stress is referred to as an imbalance between the production and elimination of reactive oxygen species (ROS), some of which are highly cytotoxic and promote tissue injury (66). Upon activation, innate immune cells secrete ROS and reactive nitrogen species (RNS) as a central part of killing invading pathogens (107). Production of ROS and RNS is, thus, an important downstream mechanism of inflammation-mediated immune responses. Several lines of evidence from rodent models suggest that infection-induced increases in fetal ROS and RNS levels may, indeed, be involved in changing development trajectories in the offspring (74, 75).

Besides its effects on oxidative stress systems, exposure to infection and the subsequent cytokine-associated inflammatory reactions further lead to the activation of the HPA axis by stimulating the release of corticotropin-releasing factor from the hypothalamus and of adrenocorticotropic hormone from the pituitary gland; this results eventually in an increase of glucocorticoid levels in the peripheral bloodstream (49). The cytokine-mediated effects on glucocorticoid secretion may be of special interest because it has been suggested that prenatal physiological stress triggered by high glucocorticoid levels can interfere with normal physiological and metabolic development (130, 156). Activation of the innate immune system (in response to infection) also changes the maternal and fetal availability of several micronutrients, including iron and zinc, both of which are highly important for the normal development of peripheral and central organs (3, 71, 72, 149). In the case of iron, it is well established that infection leads to a temporary depletion of iron in the infected host. This process is mediated to a great extent by the proinflammatory cytokines IL-1β and IL-6 (76, 109) and serves to reduce the availability of this essential nutrient to the invading pathogens as part of the host’s inherent defense system (65). As part of the acute-phase response to infection, proinflammatory cytokines also trigger the induction of the zinc-binding protein metallothionein (152).

During the course of pregnancy, this process leads to maternal and fetal zinc deficiency, which has further been associated with teratogenicity and abnormal developmental processes in utero (33, 142).

In addition to its effects on micronutrient availability, maternal infection during pregnancy may also impair the fetal supply for macronutrients. Indeed, it is well established that peripheral cytokine elevation in response to infection induces a set of behavioral and physiological changes collectively referred to as sickness behavior (32). Sickness behavior typically includes fever, malaise, and reduced exploratory, and social investigation, as well as decreased food and water intake, accompanied usually by weight loss. The effects of immune challenge on weight loss may be particularly relevant because prenatal malnutrition has also been implicated as a risk factor for various developmental disturbances (73, 84).

Finally, it should also be noted that at least part of the changes to the microbiome that emerge following prenatal infection (59) may have an early prenatal origin. The conventional view is that microbial colonization begins at birth when the neonate is first exposed to the microbiome of the mother and the surrounding environment (39, 82), implying furthermore that the fetal environment is sterile and, therefore, lacks a microbiome before birth. This view has recently been challenged by findings showing that the human placenta is not sterile but, in fact, is colonized with nonpathogenic commensal microbiota (1). Perhaps even more important are the findings suggesting that the microbial composition of the human placenta can be modified by maternal infection during pregnancy, even if the infectious process takes place during the time of conception or in early gestation (1). One important implication from these recent findings is that modifications of the placental microbiome, be it as a result of maternal infection or by other environmental factors, can critically shape the development of the offspring’s microbiome and thus predispose the developing organism to dysbiosis and other microbiome-associated abnormalities.

Defining the Next Steps

Prenatal immunological adversities, such as maternal infection, have been widely acknowledged to contribute to an
increased risk of neurodevelopmental brain disorders. Somewhat less attention has been given to the long-term consequences of prenatal infection on peripheral functions. Hence, additional work is clearly warranted to further define the putative effects of infection-related prenatal adversities on postnatal physiology and metabolism. What is perhaps most urgently needed to achieve this goal is more comprehensive evidence from human epidemiological studies. To our knowledge, only one epidemiological study has yet directly explored the putative association between maternal infection during pregnancy and increased risk of obesity in the offspring (25). Even though this study included a large number of subjects, it requires replication and further extension to other physiological and metabolic parameters. It should also be mentioned that exposures were broadly defined as “infections requiring hospitalization” in this first epidemiological study, so that the possible relevance of pathogen specificity remained unexplored. Hence, we do not know whether long-term metabolic abnormalities can similarly be induced by prenatal exposures to various infectious pathogens, or alternatively, whether this association is dependent on the precise identity of the pathogen. One powerful approach to overcome this limitation would be the use of prospective epidemiological designs, in which a specific infectious pathogen or inflammatory marker in prenatal life can be measured quantitatively. Such prospective epidemiological research has been proven indispensable for the establishment of associations between prenatal exposure to specific infectious pathogens and later risk of neuropsychiatric disease (19, 22, 116). Hence, the future identification of possible long-term effects of prenatal infection on general physiology and metabolism might strongly benefit from such prospective epidemiological research.

For ethical and technical reasons, however, human epidemiological research will not be able to establish causality for such associations and will be limited in its capacity to unravel the downstream cellular and molecular mechanisms affecting normal physiological development. The examination of epidemiologically relevant risk factors in animal models, thus, remains an important field of research to overcome these limitations. As outlined above, several animal models of prenatal immune challenge exist, so that their continuous implementation will be pivotal to extend our knowledge on pathophysiological mechanisms underlying the association between prenatal infection and peripheral abnormalities. In these attempts, a special emphasis should be placed on elucidating causal (and bidirectional) relationships between peripheral abnormalities and neurobehavioral deficits. These latter investigations may help to establish holistic therapeutic interventions with beneficial effects on both central and peripheral dysfunctions.

**Perspectives and Significance**

Several recent epidemiological and animal studies suggest that infection-related prenatal adversities can negatively affect various physiological and metabolic functions beyond those typically associated with primary defects in CNS development. These include excessive accumulation of adipose tissue and increased body weight, impaired glycemic regulation and insulin resistance, altered myeloid lineage development in favor of proinflammatory signaling, increased gut permeability, and changes in microbiota composition. The existing data suggest that these peripheral abnormalities can directly contribute to the emergence of CNS abnormalities, so that a normalization of peripheral symptoms effectively alleviates behavioral deficits induced by prenatal infection. Thus, it follows that seemingly unrelated central and peripheral effects of prenatal infection may not represent separate pathological entities, but rather, they may be considered as pieces of the same puzzle. In fact, there might be a “vicious circle” involving constant pathological interactions between developmentally acquired brain abnormalities and peripheral dysfunctions, in which deficient peripheral functions facilitate or maintain CNS abnormalities, and vice versa. Thus, targeting peripheral abnormalities may represent a valuable strategy to improve the multitude of behavioral abnormalities that can emerge in subjects with prenatal infectious histories.

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the authors.

**AUTHOR CONTRIBUTIONS**

Author contributions: M.A.L. and U.M. prepared figures; M.A.L. and U.M. drafted manuscript; M.A.L., W.L., and U.M. edited and revised manuscript; M.A.L., W.L., and U.M. approved final version of manuscript.

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