
Unraveling the intricacy of maternal immune activation and offspring brain development: A matter of time

Response to: *Maternal Infection and the Offspring Brain* by Amaicha Mara Depino

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Considerable epidemiological evidence suggests an appreciable association between maternal viral or bacterial infections and higher risk for neuropsychiatric disorders of a presumed neurodevelopmental origin in the offspring (see recent reviews by Brown and Susser, 2002; Arndt et al, 2005). Recent manipulative experimentation in animals has demonstrated a causal link between maternal/prenatal immune challenge and the emergence of brain and behavioral pathology in later life. Our latest attempt in characterizing the long-term structural and functional consequences of prenatal inflammatory events induced by polyriboinosinic-polycytidylic acid (PolyI:C) indicates that this link is critically determined by the precise prenatal timing (Meyer et al, 2006a,b) as lucidly reviewed by Dr. Amaicha Depino.

Our experimental demonstration in mice of the temporal dependency of the prenatal infection’s effect on neurodevelopment strongly supports the epidemiologically based hypothesis that specific gestational periods may correspond to time windows with varying vulnerability to infection-mediated neurodevelopmental disturbances associated with distinct adult psychopathology.

Retrospective epidemiological investigations initially suggested that a higher incidence of schizophrenia is maximally associated with infectious processes taking place in the second trimester of human pregnancy, and that this period represents the maximal vulnerability to neurodevelopmental disturbances (reviewed in Brown and Susser, 2002). This view has since been challenged by prospective epidemiological studies showing that the critical gestational period may be earlier (in the first weeks of gestation) rather than around mid-pregnancy as previously thought.

The correspondence of fetal developmental progression between human and rodents however remains controversial. This highlights the difficulty in equating the windows identified in laboratory rodents to human epidemiological studies, and vice versa. Such approximation is also debatable between closely related species, such as rats and mice. Early (pre- and postnatal) development of the central nervous system (CNS) follows a tightly regulated time course marked by discrete phases of proliferation, migration, differentiation, target selection and maturation of different neuronal and glial populations. Although the sequence may be comparable, the precise timing of these events may vary considerably between species. For example, many key neurodevelopmental events in the mouse occur approximately two days earlier than in rats (Bayer et al, 1995). Thus, it is not surprising that an immunological challenge may result in dissimilar patterns of pathology in mice and rats even when it is timed at the same gestation day (GD): perseverative behavior was observed in adult mice derived from dams having been exposed to PolyI:C on GD17 (Meyer et al, 2006b), while increased switching behavior was reported in rats following prenatal immunological stimulation on the same GD (Zuckerman and Weiner, 2005). A better understanding of the critical neuro-immunological factors underlying the species difference between rats and mice would be indispensable to further cross-species comparisons to humans.

Given that the link between maternal infections and emergence of adult psychopathology (schizophrenia and related disorders) appears to be independent of the precise identity of the pathogenic agent, factors common to all infections must contribute to causal mechanism involved. The release of cytokines by the maternal host, and subsequent cytokine elevations in the fetal brain, may thus represent a key immunological event linking maternal infections to neurodevelopmental disturbances that in turn give rise to postnatal psychopathology. Besides their immunological roles, cytokines can directly interfere or precipitate mal-development of the CNS with long-term pathological...
consequences. In addition, cytokine-associated stimulation of the peripheral immune system is accompanied by the activation of the stress response axes, including the generation of sickness behavior. Inflammation-induced maternal physiological and/or psychological stress during pregnancy can result in deviant maternal-infant interaction and provides another route whereby cytokine elevation can interfere with early life neurodevelopment of the offspring. Maternal stress during pregnancy has been shown to induce long-term disturbance in postpartum maternal behavior (Meek et al, 2001; Weinstock, 2005), thus subjecting the neonate to an unfavorable rearing environment.

We have recently initiated cross-fostering studies to elucidate the relative contributions of prenatal inflammatory events and postnatal maternal factors in precipitating psychopathology in the resulting offspring (Meyer et al, 2006c). Latent inhibition deficits were observed in offspring born to dams having been challenged with PolyI:C at mid-gestation regardless of whether they were raised by a dam having received PolyI:C challenge during pregnancy or not. Hence, the adoption of offspring born to treated dams by untreated dams did not prevent the emergence of this psychosis-related adult psychopathological phenotype. Although this finding does not exclude the involvement of aberrant fetal brain levels of stress-associated molecules (e.g. corticotropin releasing hormone; see Gayle et al, 2004), our cross-fostering study (Meyer et al, 2006c) supports the hypothesis that inflammation-mediated disruption of fetal brain development can account for the emergence of some psychopathological traits in later life. On the other hand, pre- and post-pubertal learning deficits (in the form of impaired aversive conditioning) were noted in prenatal control mice that were raised by immune-challenged surrogate mothers (Meyer et al, 2006c). This highlights that the adoption of prenatal control animals by immune-challenged rearing mothers is sufficient to induce learning disabilities that can already be detected at the juvenile age. This causal link emphasizes the importance of post-partum maternal-infant interaction to normal brain development. Although largely unknown, the mechanisms involved here should be distinct from those associated with direct cytokine-mediated interference in neurodevelopmental processes.

Finally, we wish to emphasize that the prenatal immune activation models in animals provide a holistic approach to study the intricate interactions among the immune system, the development/maturing of the nervous system, and relevant external environmental factors in the etiology of schizophrenia and related disorders. Their continual evaluation and examination are expected to reveal multiple neuropathological mechanisms, with further specifications to the long-term structural and functional consequences related to immuno-activation at distinct periods of fetal development, as well as the roles of selected cytokines and related molecules. Since the behavioural contrast between early/mid and late pregnancy immune activation may be related to the positive-negative symptoms dichotomy in schizophrenia (Sullivan et al, 2006), the prenatal immune activation models may yield important new insights into the segregation of postnatal symptom clusters from a neurodevelopmental perspective.

(989 words)

References

