Fever Results from a Cross Talk between the Immune and the Nervous System

Fever is often confused with hyperthermia. While hyperthermia refers to a passive increase in body temperature, fever is the result of a regulated increase in the thermoregulatory set point [1]. Several studies strongly suggest that the thermoregulatory center is located in the preoptic region of the hypothalamus [2, 3]. The most commonly used model of experimental fever involves a systemic injection of lipopolysaccharide (LPS), an active ingredient of the outer membrane of Gram-negative bacteria which activates immune competent cells [4]. Upon LPS binding to its receptor complex composed of toll-like receptor 4 (TLR4) and CD14 [5–7], a cascade of intracellular signaling pathways is activated, culminating in the translocation of the nuclear factor κB (NFκB) from the cytoplasm into the nucleus [8, 9]. NFκB binds to the promoter regions of several proinflammatory genes including interleukin (IL)-1β, IL-6, and tumor necrosis factor-α (TNF-α) and induces their expression [10]. A large body of evidence suggests that the proinflammatory cytokines or their secondary signals access the fever-controlling region of the hypothalamus via either hormonal or neuronal pathways [11–13]. This immune-to-brain signaling leads to the induction of cyclooxygenase type 2 (COX-2)
within the preoptic area of the hypothalamus [14, 15]. COX-2 is the rate-limiting enzyme for the synthesis of prostaglandin of the E₂ series (PGE₂). Once produced, PGE₂ binds to its E-prostanoid receptor type 3 (EP3) located in the preoptic area of the hypothalamus [16–18]. PGE₂-EP3 interaction leads to a reduced GABAergic inhibitory tone and an enhanced glutamatergic stimulatory effect on heat production from brown adipose tissue [19].

While the proinflammatory cytokines are involved in the initiation of fever, they also activate an anti-inflammatory pathway via a concerted action on the hypothalamic-pituitary-adrenal (HPA) axis [10, 20, 21]. Cortisol (corticosterone in rodents), the end product of HPA axis activity, is known to dampen inflammation and its resulting febrile response [22–24], likely via an inhibitory action on the NFκB signaling pathway [25]. In addition to the anti-inflammatory effect of cortisol, anti-inflammatory cytokines such as IL-4 and IL-10 [26–29] and neuropeptides such as vasopressin are also known as endogenous antipyretics [30–32].

**Neonatal Immune Challenge Alters Adult Fever**

Fever is regarded as a malaise that needs to be ‘treated’. However, it is now accepted that fever is an adaptive response to pathogens. It creates a conducive environment to help the immune system fight off the infection [1, 33]. Thus, any alteration in the ability to mount an appropriate febrile response could have a negative health impact. A large body of evidence strongly suggests that early life experience with pathogens could ‘reprogram’ the febrile response to pathogens encountered during adulthood.

The indication that early life immune challenge could alter the febrile response in adults stemmed from a series of studies showing that injection of a mild dose of LPS into neonatal rodents leads to an enhanced HPA axis activity during adult life [34–36]. Because corticosterone, the end product of HPA axis activity, dampens fever, it was hypothesized that a neonatal immune challenge could alter the adult fever response. Indeed, LPS administration to rats during the neonatal period led to a dampened febrile response to LPS when these animals reached adulthood [37–42]. The programming effect of an early life immune challenge on fever seems to be dependent on the developmental stage at which the immune system was initially mobilized. LPS injection on either postnatal day (PND) 7 or PND28 did not alter adult LPS fever, but administration of LPS on PND14 or PND21 attenuated adult LPS fever [43]. Interestingly these attenuated febrile responses were associated with blunted LPS-induced COX-2 expression in the fever-controlling regions of the hypothalamus [40, 43].

These long-lasting effects were also accompanied by an enhanced, albeit transient, adult HPA axis responsiveness to LPS. This enhanced HPA axis responsiveness was lost when adult animals were subjected to adrenalectomy combined with a constant supply of physiological doses of corticosterone or when adult rats were given RU486, a glucocorticoid receptor antagonist [39]. Similarly, the heightened HPA activity led to attenuated levels of circulating proinflammatory cytokines (IL-β, IL-6, and TNF-α) [39] and to reduced levels of their gene expression in the hypothalamus [44], likely through a reduced activity of the NFκB signaling pathway [39]. These attenuated cytokine responses were also abolished by either adrenalectomy or blockade of glucocorticoid receptors [39]. Thus, it seems that the long-lasting impact of an early life immune challenge on the adult febrile response is strongly linked to the heightened HPA responsiveness.

**Homotypic versus Heterotypic Stimulations**

The programming effect of neonatal immune challenge is not limited to bacterial LPS. In fact, early life exposure to the viral mimetic polyinosinic-polycytidylic acid (Poly I:C), a TLR3 activator, also dampened adult Poly I:C-induced fever and resulted in an upregulated HPA axis response to TLR3 activation during adulthood [37]. It is now clear that the HPA axis is at the center of the programming effects of TLR3 and TLR4 activations. Thus, one could assume that neonatal immune activation of TLR4 (with LPS) leads to a heightened HPA axis responsiveness and would consequently dampen the adult fever response to TLR3 activation and vice versa. This was not the case. Early life exposure to Poly I:C did not affect adult LPS-induced fever. Inversely, neonatal exposure to bacterial LPS did not affect Poly I:C-induced fever in adults [37]. The requirement of this homotypic stimulation is further supported by the lack of an LPS programming effect on adult IL-1β-induced fever [40]. In order to sustain this long-lasting programming effect on fever, it seems necessary that the same receptor (e.g. TLR3 or TLR4) should be activated at both neonatal and adult ages. Thus, these homotypic stimulations (LPS-LPS or Poly I:C-Poly I:C) effects may operate through a specific action on their own signaling pathways [6, 9, 45]. Finally, it is interesting to note that early life injection of a non-lethal dose of live *Escherichia coli* does not impact adult
Perinatal Immune Stress Programs the Adult Febrile Response

Prenatal Immune Challenge and the Innate Immune Response

Prenatal immune challenge also results in altered HPA axis activity in adult offspring [48], which could impact the adult febrile response. Few studies have addressed this question. LPS injection in sheep during the last period of pregnancy (during the last month of gestation) increased corticosterone levels and dampened their eyes’ temperature response to a subsequent LPS injection at a juvenile age [49]. Similarly, adult offspring of pregnant guinea pigs given repeated LPS injections in the last phase of pregnancy showed a reduced LPS-induced fever 3 h after LPS administration [50]. Surprisingly, data on the long-lasting effects of prenatal immune challenge in rats were missing. We recently explored the possibility that prenatal immune challenge impacts the adult rat febrile response. LPS administration to dams on gestational day (GD) 15 resulted in a significant reduction in LPS fever in adult offspring. Such an effect was absent if the dams were given LPS on either GD12 or GD19. Interestingly, the adult corticosterone response to LPS was transiently but significantly enhanced while COX-2 induction in the fever-controlling region of the hypothalamus was reduced specifically in offspring born to dams given LPS on GD15 [51].

It is unclear whether this enhanced corticosterone response would lead to a dampened production of inflammatory cytokines. However, serum levels of IL-1β, IL-6, and TNF-α induced by LPS as well as LPS-induced mRNA of inflammatory cytokines in the brains of 3-week-old rats were reduced in those born to dams given LPS on GD18 [52]. Repeated prenatal LPS injections (on GD16, GD18, and GD20) also resulted in reduced LPS-induced TNF-α, but no significant change in LPS-induced IL-1β was observed [53]. Thus, the dampened innate immune response in adult offspring born to immune challenged dams during pregnancy could underlie the reduced febrile response.

More than Just Fever Programming

A substantial amount of knowledge has been accumulated on the long-lasting impact of perinatal immune challenge on many physiological parameters. Aside from the HPA axis alteration, perinatal immune challenge has broader effects on brain development and plasticity. Experimentally, early life immune stimulation has been shown to impact several pathophysiological parameters such as alteration of pain perception [54], impairments in learning and memory [55–57], brain cell death secondary to ischemia [58], loss of dopaminergic neurons in the nigrostriatal brain area (a phenomenon strongly associated with Parkinson’s disease) [59, 60], susceptibility to seizures [61], exacerbation of experimental colitis [62], and suppression of experimental autoimmune encephalomyelitis, an experimental model of multiple sclerosis [63]. Despite this large amount of experimental evidence on the long-lasting and profound impact of early life immune challenge, we still do not know how these ‘imprinting’ processes are triggered, nor do we have a good understanding of how they last throughout life. More research is needed to explore the mechanisms through which an early life immune challenge leaves a permanent pathophysiological ‘trace’ in developing brains. One such promising research avenue is the lasting nongenomic modification termed epigenetic [64–66]. Indeed, early life challenges such as stress and poor nutrition or levels of maternal care could ‘permanently’ turn on or off some genes via acetylation or methylation of their promoter regions [67–72]. It is conceivable that a permanent alteration in the expression of such genes could form the basis for a sustained change in the set point of different physiological parameters and could explain the lasting impact of early life experiences on brain function and plasticity [65, 73, 74]. Interestingly, some of these epigenetic modifications could be ‘passed on’ to offspring, thus allowing these genetic modifications to potentially last into future generations for, perhaps, their adaptive values [75, 76]. Whether an early life immune challenge exerts its long-lasting effects via epigenetic modifications is still an open question.

Conclusion

Fever is an adaptive response to infection. Any alteration of the febrile response can lead to deleterious effects. While exposure to pathogens invariably leads to alteration of the thermoregulatory set point, the magnitude of the fever response can be permanently programmed by
early life exposure to viral and bacterial pathogens. This programming effect occurs during both pre- and postnatal periods when the brain areas involved in thermoregulation are emerging and/or maturing. It has been repeatedly observed that early life exposure to pathogens permanently heightens HPA axis activity. Aside from its impact on the febrile response, this enhanced HPA axis contributes to a myriad of pathophysiological conditions. Future studies should explore whether the programming effects of early life immune challenge are sustained by epigenetic modifications of genes required for the thermoregulatory response (e.g. }\textit{cox}-2) or are due to permanent plastic changes in the brain areas/structures involved in the neuroimmune responses.

Acknowledgment

Parts of this work were performed in the laboratory of Dr. Abdeslam Mouihate and were supported by Kuwait University research grant No. MY01/09. The author wishes to thank Dr. Samuel B. Kombian for reading the manuscript.

Disclosure Statement

The author declares that no financial or other conflict of interest exists in relation to the content of the article.

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