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Inflammation-induced fever depends on prostaglandin E2 production by brain endothelial cells and EP3 receptors in the median preoptic nucleus of the hypothalamus

Anders Blomqvist

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Inflammation-induced fever depends on prostaglandin E2 production by brain endothelial cells and EP3 receptors in the median preoptic nucleus of the hypothalamus: Comment on Bai, Acta Physiol, 2024(9): p. e14225 and Yu et al., Acta Physiol, 2024. 240(9): p. e14187.

Anders Blomqvist

Division of Neurobiology, Department of Biomedical and Clinical Science, Linköping University,
581 85 Linköping, Sweden

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Correspondence: Anders Blomqvist, address as above. E-mail: anders.blomqvist@liu.se

To the Editor: I read with interest the editorial by Xianshu Bai [1] on the paper by Yu et al. [2] on the role of caspase 11 in fever. However, I feel that the author ignores the absolutely critical role that prostaglandin (PG) E₂ production in brain endothelial cells has in generating fever, rather considering it as an auxiliary mechanism. Although both peripheral and central cytokine production may contribute to fever, as suggested by the study by Yu et al. [2], the critical mechanism is PGE₂ synthesis and its binding to EP₃ receptor neurons in the median preoptic nucleus (MnPO) of the hypothalamus [3, 4]. If PGE₂ synthesis is blocked or EP₃ receptors deleted in the MnPO, no fever occurs [5, 6], even though there still is increased cytokine production in the periphery and in the brain [7]. The critical PGE₂ synthesis occurs in brain endothelial cells as shown by the absence of fever when the PGE₂ synthesizing enzymes cyclooxygenase-2 (Cox-2) and microsomal prostaglandin E synthase-1 (mPGES-1) are deleted from these cells [8]. Cox-2 and mPGES-1 are in turn induced by cytokine binding to receptors on the endothelial cell [9-11] (Fig. 1). If these receptors, such as those for IL-1 and IL-6, or their downstream signaling molecules are selectively deleted from brain endothelial cells, the fever is suppressed [12-15].

It should also be pointed out that the evidence for the involvement of microglial cells in inflammation induced sickness responses, and in particular in fever, is far from clear. Although it is well recognized that peripheral inflammation activates microglial cells [16], the mechanism behind this activation is not fully understood. It is unlikely due to direct action of cytokines on the microglial cells, particularly when it comes to interleukin-1, which is a major pyrogen [17], because if transport across the blood-brain barrier at all occurs in any significant amount, microglial cells express negligible levels of IL-1 receptors [18]. The critical IL-1 receptor-expressing cells for IL-1 activation of microglial cells are the endothelial cells, which via an as-yet-unidentified messenger molecule by a paracrine mechanism activate the microglial cells [19].

While it is generally assumed that various sickness symptoms and neuropsychiatric disorders are associated with activated microglia [20], apart from a study demonstrating a role of striatal microglial cells in negative affect elicited by peripheral inflammation [21], there is very little evidence for a causal relationship between these phenomena. It is not even clear which brain cells are responsible for the increased levels of cytokines seen after peripheral inflammation. When microglial cells were depleted, LPS-induced cytokine expression in the brain was unaffected, as were disease symptoms such as body weight loss and suppressed motor activity [22]. The role of activated microglia in fever has not, to my knowledge, been investigated before.

Although the study by Yu et al. [2] suggests that microglial cells contribute to the fever response, there are several caveats that need to be considered. In one set of experiments the authors used intracerebral injection of clodronate to delete microglial cells. However, clodronate also appears to target perivascular macrophages, as was shown by Schiltz and Sawchenko [23], and while the clodronate injection reduced the response to peripheral injection of IL-1, as shown in a subsequent study from the Sawchenko laboratory [24], it enhanced the response, including fever, to peripheral injection of LPS, i.e. a finding opposite to that reported by Yu et al. [2]. In another set of experiments Yu et al. injected into the preoptic region an adenovirus expressing shRNA to silence the caspase 11 expression through RNA interference. Although they report reduced caspase 11 expression in microglia but not in neurons (and associated attenuated fever) they do not seem to have examined the extent to which caspase 11 expression was attenuated in other cell types such as perivascular macrophages and endothelial cells.

In conclusion, I feel that the findings by Yu et al. [2], and in particular the idea the febrile response is enhanced by preoptic microglia, although interesting, should be interpreted with caution. And importantly, even if there were indeed such an enhancement of the fever signal, according to the evidence available today, such an enhanced signal would still need to be converted into PGE₂ synthesis by brain endothelial cells in order to augment the fever response.

It is in this context of interest to note in the study by Yu et al. [2] that both the intracerebral chlodronate injection to deplete microglia and the RNA interference to silence caspase 11 were reported to result in decreased concentrations of PGE₂ in the brain, implying that the mechanism described indeed would be upstream of PGE₂ synthesis.

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Legend to figure

Fig. 1. IL-1 and IL-6 elicit PGE₂ synthesis in brain endothelial cells via IL-1 receptor type 1 (IL-1R1) and IL-6 receptor α (IL-6R) and Tak1/NfκB and STAT3 signaling, respectively. The PGE₂ binds to receptor on thermoregulatory neurons in the median preoptic nucleus (MnPO) (from [25]).

