

Review

Cytokines, PGE₂ and endotoxic fever: a re-assessment

Clark M. Blatteis^{*}, Shuxin Li, Zhonghua Li,
Carlos Feleder, Vit Perlik

*Department of Physiology, College of Medicine, The University of Tennessee, Health Science Center,
894 Union Avenue, Memphis, TN 38163, USA*

Received 4 January 2005; accepted 8 January 2005

Available online 19 February 2005

Abstract

The innate immune system serves as the first line of host defense against the deleterious effects of invading infectious pathogens. Fever is the hallmark among the defense mechanisms evoked by the entry into the body of such pathogens. The conventional view of the steps that lead to fever production is that they begin with the biosynthesis of pyrogenic cytokines by mononuclear phagocytes stimulated by the pathogens, their release into the circulation and transport to the thermoregulatory center in the preoptic area (POA) of the anterior hypothalamus, and their induction there of cyclooxygenase (COX)-2-dependent prostaglandin (PG)E₂, the putative final mediator of the febrile response. But data accumulated over the past 5 years have gradually challenged this classical concept, due mostly to the temporal incompatibility of the newer findings with this concatenation of events. Thus, the former studies generally overlooked that the production of cytokines and the transduction of their pyrogenic signals into fever-mediating PGE₂ proceed at relatively slow rates, significantly slower certainly than the onset latency of fever produced by the i.v. injection of bacterial endotoxic lipopolysaccharides (LPS). Here, we review the conflicts between the earlier and the more recent findings and summarize new data that reconcile many of the contradictions. A unified model based on these data explicating the generation and maintenance of the febrile response is presented. It postulates that the steps in the production of LPS fever occur in the following sequence: the immediate activation by LPS of the complement (C) cascade, the stimulation by the anaphylatoxic C component C5a of Kupffer cells, their consequent, virtually instantaneous release of PGE₂, its excitation of hepatic vagal afferents, their transmission of the induced signals to the POA via the ventral noradrenergic bundle, and the activation

^{*} Corresponding author. Tel.: +1 901 448 5845; fax: +1 901 448 1673.

E-mail address: blatteis@physio1.utm.edu (C.M. Blatteis).

by the thus, locally released norepinephrine (NE) of neural α_1 - and glial α_2 -adrenoceptors. The activation of the first causes an immediate, PGE₂-independent rise in core temperature (T_c) [the early phase of fever; an antioxidant-sensitive PGE₂ rise, however, accompanies this first phase], and of the second a delayed, PGE₂-dependent T_c rise [the late phase of fever]. Meanwhile-generated pyrogenic cytokines and their consequent upregulation of blood–brain barrier cells COX-2 also contribute to the latter rise. The consecutive steps that initiate the febrile response to LPS would now appear, therefore, to occur in an order different than conceived originally.

© 2005 Elsevier Inc. All rights reserved.

Keywords: Prostaglandin (PG)E₂; Cyclooxygenase (COX)-1 and -2; Prostaglandin E synthases (PGES); Phospholipases (PL); Complement (C) 5a; Mononuclear phagocytes; Kupffer cells (Kc); Vagus; Norepinephrine (NE); α_1 - and α_2 -Adrenoceptors (AR); Preoptic-anterior hypothalamus (POA); Nitric oxide (NO); Lipopolysaccharides (LPS); Organum vasculosum laminae terminalis (OVLT); Microcerebrovascular endothelial cells

Contents

1. Introduction	2
2. The classical pyrogenic signaling pathway	3
3. The inconsistencies	4
3.1. The temporal incompatibility of the cytokines	4
3.2. The improbability of direct triggering by LPS	5
3.3. The disputed source of PGE ₂	6
4. An alternative signaling pathway	6
5. The dual roles of PGE ₂	9
5.1. In the periphery	9
5.2. In the POA	10
6. Conclusions	12
Acknowledgements	12
References	12

1. Introduction

Although the role of prostaglandin (PG)E₂ in fever production was not immediately accepted ipso facto after Milton and Wendlandt reported in 1971 [1] that its intra-cerebral microinjection evokes a prompt rise in the recipients' body (core) temperatures (T_c) and Vane [2] demonstrated that aspirin blocks prostaglandin synthesis, it has now become axiomatic that this lipid mediator is pivotally involved in the febrile response to infectious pathogens. Thus, it is now generally believed that cyclooxygenase (COX)-2 and microsomal prostaglandin E synthase (mPGES)-1 selectively induced by pyrogenic cytokines catalyze its production, and that it acts in the preoptic-anterior hypothalamus (POA), the brain site of the primary thermoregulatory controller [3–5]. Indeed, the accumulated evidence is compelling [6–10]: (a) PGE₂ almost immediately raises T_c when microinjected

Download English Version:

<https://daneshyari.com/en/article/9894076>

Download Persian Version:

<https://daneshyari.com/article/9894076>

[Daneshyari.com](https://daneshyari.com)