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Research Report

Cytokines, but not corticotropin-releasing factor and endothelin-1, participate centrally in the febrile response in zymosan-induced arthritis in rats

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ABSTRACT

Recent literature has revealed that centrally generated prostaglandins participate in the febrile response in zymosan-induced arthritis in rats. However, it is not clear whether other centrally acting pyrogenic mediators such as cytokines, endothelins (ETs), and the corticotropin-releasing factor (CRF) contribute to the febrile response in this model. In the present study, rats were pretreated with intracerebroventricular (i.c.v.) injections of soluble TNF receptor I (sTNFRI), recombinant IL-1 receptor antagonist (IL-1ra), anti-rat IL-6 monoclonal antibody (AbIL-6), α-helical $CRF_{9–41}$ (a nonselective CRF_1/CRF_2 receptor antagonist), BQ-123 (an ET_A receptor antagonist), BQ-788 (an ET_B receptor antagonist), and artificial cerebrospinal fluid (aCSF, control) prior to an intra-articular zymosan (4 mg) injection. Rectal temperatures were measured with a telethermometer. The administration of IL-1ra (200 μg), sTNFRI (500 ng), and AbIL-6 (5 μg) attenuated body temperature elevations after a zymosan injection. The administration of BQ-788 (3 pmol), BQ-123 (3 pmol), and α-helical CRF_{9-41} (25 μg) did not affect the zymosan-induced febrile response. All the compounds used to pretreat the animals did not significantly alter their basal body temperatures. Together, the results here demonstrate that the febrile response in zymosan-induced arthritis in rats depends on the centrally acting pyrogenic cytokines TNF-α, IL-1β, and IL-6, but does not depend on either CRF or ET-1.

Abbreviations: AbIL-6, anti-rat IL-6 monoclonal antibody; ANOVA, analysis of variance; aCSF, artificial cerebrospinal fluid; CRF, corticotropin-releasing factor; ET, endothelin; i.a., intra-articular; i.c.v., intracerebroventricular; i.pl., intra-plantar; IL, interleukin; IL-1ra, IL-1 receptor antagonist; LPS, lipopolysaccharide; PGE_2, prostaglandin E_2; SEM, standard error of the mean; sTNFRI, soluble TNF receptor I; TNF, tumor necrosis factor.

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1. Introduction

Fever is an event of the acute-phase response that can be defined as the controlled elevation in body temperature in response to tumors, inflammation, invading microorganisms, and microbial components like lipopolysaccharide (LPS) from *E. coli* and zymosan (an insoluble polysaccharide from the *Saccharomyces cerevisiae* cell wall) (Roth and De Souza, 2001; Kanashiro et al., 2009). These stimuli elicit the generation of endogenous mediators that change the hypothalamic thermal set point at the preoptic area. Such change characterizes fever as a physiological neuro-endocrine-immune response (Blatteis, 2006; Roth and De Souza, 2001).

During infectious processes, fever protects the organism by stimulating innate and adaptive immune system cells to produce antibodies and by phagocytizing and clearing the invading pathogens. Fever also activates immune cells to destroy tumor cells, thus reducing the tumor growth rate (Peterson et al., 1977). Although the febrile response is physiologically beneficial, it may cause serious clinical complications in patients suffering from non-infectious diseases such as inflammatory and autoimmune diseases (Moltz, 1993; Zeisberger, 1999).

Rheumatoid arthritis, an autoimmune inflammatory disease that affects 0.5–1% of the population worldwide, is characterized by a chronic synovial membrane inflammation (Firestein, 2003). Fever is an extra-articular manifestation that can occur during the onset and development of rheumatoid arthritis (Grassi et al., 1998). Investigations into how pro-inflammatory mediators contribute to rheumatoid arthritis pathogenesis may help to develop therapeutic strategies to control the febrile response in rheumatoid arthritis patients.

In experimental animals, intra-articular zymosan injections promote local and systemic inflammatory responses. Pain and edema are the main characteristics of local inflammation, while the long-lasting body temperature elevation is one of the hallmarks of systemic inflammation (Kanashiro et al., 2009). A decrease in tail skin temperature followed by a rectal temperature increase are important physiological signs of the increase in body temperature that occurs during the integrated febrile response elicited by a zymosan injection (Kanashiro et al., 2009; Gordon et al., 2002). This febrile response lasts 10 h, and it is (i) independent of neural pathways, as evaluated by the sciatic nerve excision, (ii) associated to augmented central prostaglandin E_2 (PGE_2) concentration, and (iii) sensitive to antipyretic drugs (Kanashiro et al., 2009).

A number of researchers have reported that central pyrogenic mediators participate in the febrile response induced by systemic LPS administration. Cytokines like the tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6, as well as the corticotropin-releasing factor (CRF) and endothelin-1 (ET-1) constitute other classes of mediators that act on the central nervous system triggering the fever after LPS injection. (Lundkvist et al., 1996; Fabricio et al., 1998; Konsman et al., 2008; Harden et al., 2008; Figueiredo et al., 2010). However, the roles that these mediators play in the febrile response in rheumatoid arthritis remain to be determined. Based on these facts, the present study aims to investigate whether central cytokines, CRF, and ET-1 are involved in the febrile response induced by intra-articular zymosan injections into rat knee joints.

2. Results

2.1. *The cytokines TNF-α, IL-1β, and IL-6 are essential to the febrile response in zymosan-induced arthritis*

The i.c.v. administration of TNF-α (250 ng), IL-1β (3.12 ng), and IL-6 (300 ng) elicited a rapid and long-lasting increase in body temperature (Figs. 1–3A, respectively). This increase peaked at 1.5 h (for TNF-α and IL-1β) or 2 h (for IL-6) after the cytokine injection. Zymosan (i.a.; 4 mg per joint) elicited a slow but marked elevation in body temperature that started around 3 h and peaked at 4–5 h after the injection (Figs. 1–3B).

Rats were pretreated with sTNFRI (500 ng; i.c.v.), IL-1ra (200 μg; i.c.v.), and AbIL-6 (5 μg; i.c.v.), at doses that significantly reduced the elevation of body temperatures induced by TNF-α (Fig. 1A), IL-1β (Fig. 2A), and IL-6 (Fig. 3A), respectively, also reduced zymosan-induced fever (Figs. 1–3B, respectively). The ΔT (°C) values of the groups pretreated with sTNFRI, IL-1ra, and AbIL-6 and further treated with zymosan were significantly different from the ΔT (°C) values obtained for control group (saline/zymosan) 4.5 h, 4.0 h, and 5.0 h after the zymosan injection, respectively (Figs. 1–3B).

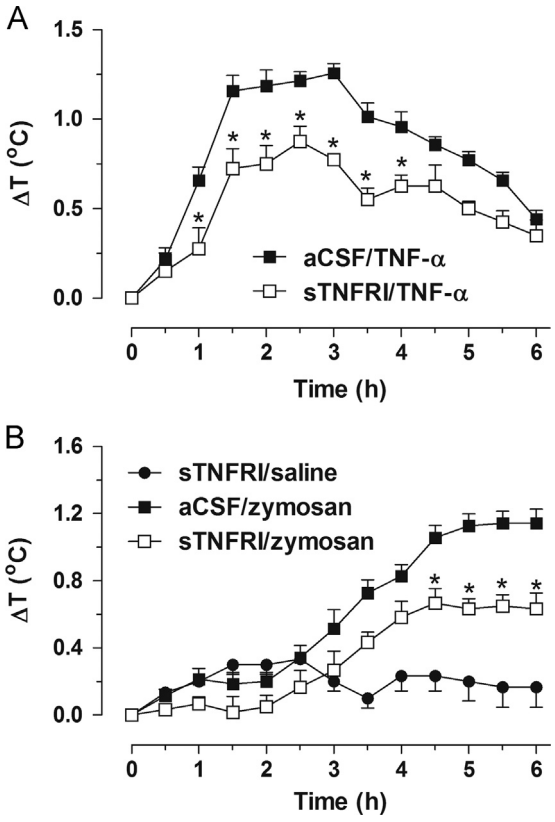

Fig. 1 – Effect of pretreatment with sTNFRI on fever induced by TNF-α (A) or zymosan (B). Rats received sTNFRI (500 ng; i.c.v.) 15 min prior to TNF-α (250 ng; i.c.v.) (A) or zymosan (4 mg; i.a.) (B) injection. Values represent the mean ± SEM of body temperature variation (ΔT, °C) of 6–7 animals per group. Basal body temperatures before treatment of each group were: (A) 37.00 ± 0.10 °C (□) and 36.93 ± 0.05 °C (■), (B) 37.02 ± 0.12 °C (□), 36.91 ± 0.01 °C (■), and 36.90 ± 0.03 °C (●). *$p < 0.05$ compared with aCSF/TNF (A) or aCSF/zymosan (B) groups.