
**Fever** is an ancient host-defense response and a common symptom of infection and systemic inflammation. Since Milton and Wendlandt [1] discovered the pyrogenic activity of prostaglandins (PGs) of the E series, and Vane [2] found that nonsteroidal anti-inflammatory drugs block fever by inhibiting PG synthesis, it has been accepted that fever is mediated by PGs, specifically **PGE2** [3–6].

**PGE2 synthesis** occurs in three steps: (1) membrane phospholipids are converted to arachidonic acid by phospholipase A2 (PLA2); (2) arachidonic acid is converted to PGH2 by cyclooxygenase (COX); and (3) PGH2 is isomerized to PGE2 by a terminal PGE synthase (PGES) [6,7]. It has been shown in rats [8–14] and mice [15,16] that COX-2 and microsomal PGES-1 (mPGES-1) are transcriptionally up-regulated in endothelial and perivascular cells of brain microvessels between 1.5 and 12 h after administration of pyrogenic doses of bacterial lipopolysaccharide (LPS). Furthermore, Scammell et al. [17] have shown that microinjection of the COX inhibitor ketorolac into the preoptic region attenuates the febrile response over 1.5–6 h after intravenous (i.v.) injection of LPS in rats. These results indicate that febrilegenic **PGE2** is produced centrally.

It should be considered, however, that the initiation of fever precedes by approximately 1 h the earliest time point at which PGE2-synthesizing enzymes have been shown to be up-regulated in the brain. In a thermoneutral environment, i.v. LPS typically causes in rats and mice a polyphasic fever, and the first phase of this response starts at approximately 0.5 h post-LPS [18,19]. Because the first phase is sensitive to ambient temperature and can be readily masked by the stress hyperthermia associated with animal handling and LPS injection [19,20], this phase often escapes detection and remains the least studied component of the febrile response. The first phase of LPS fever was not investigated in any of the abovementioned studies of the source of febrigenic PGE2.

We [21–23] and others [24–26] have hypothesized that, unlike the second and subsequent febrile phases, the first phase of fever is triggered by peripherally produced PGE2. Over the last two decades, several studies have attempted to test this hypothesis, but the results obtained have been inconclusive, contradictory, or incomplete (for details, see **Results and Discussion**). In particular, the location (inside or outside the brain) and phenotypes of the cells involved in the initiation of fever are unknown, as are the steps of the PGE2-synthesizing cascade that are initially activated to trigger the fever response. By closing these gaps, the present study identifies the cellular and molecular bases of the initiation of fever.