Introduction sample 2: Cellular and Molecular Bases of the Initiation of Fever. Steiner et al. (2006) PLoS Biol 4(9): e284

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 febrigenic **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.

Francoise Chanut 9/26/06 10:42 PM
Comment: Broad statement of the overall topic of the paper. Top of the funnel.

Francoise Chanut 9/26/06 10:43 PM
Comment: Rapid narrowing to the specific topic of the paper: PGE2. Note the placement of PGE2 at the end (=power position) of both the sentence and the paragraph

Francoise Chanut 9/26/06 10:47 PM
Comment: First background paragraph. The topic sentence is not at the beginning, but at the end, which works well in this case. This paragraph describes what is known.

Francoise Chanut 9/26/06 10:48 PM
Comment: Note the use of the power position to deliver the take-home message of this paragraph.

Francoise Chanut 9/26/06 10:57 PM
Comment: Second paragraph of background, describing what is not so well known/understood.

Francoise Chanut 9/26/06 10:50 PM
Comment: Transition word that signals contrast/nuance…

Francoise Chanut 9/26/06 10:51 PM
Comment: Signal of a gap in our knowledge, hence a need to fill the gap.

Francoise Chanut 9/26/06 10:52 PM
Comment: Concluding sentence that brings back PGE2 in the context of the early febrile phase.

Francoise Chanut 9/26/06 10:54 PM
Comment: Last paragraph: the hypothesis and the approach.

Francoise Chanut 9/26/06 10:53 PM
Comment: Clear statement of the hypothesis this paper is testing.

Francoise Chanut 9/26/06 10:56 PM
Comment: Signals a refinement of the question/hypothesis.

Francoise Chanut 9/26/06 10:56 PM
Comment: Subtle (too subtle perhaps) mention of the methodology. Closing the gaps means identifying the cells and enzymatic steps of early PGE2 synthesis…