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PATHOPHYSIOLOGY OF FEVER: ETIOLOGICAL FACTORS, THERMOREGULATORY MECHANISMS, STAGES, AND CLINICAL SIGNIFICANCE

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Abstract. Fever (pyrexia) represents a highly complex, systemic evolutionary-adaptive pathophysiological response of the thermoregulatory center to endogenous and exogenous pyrogens. Characterized by a controlled elevation of core body temperature, fever differs fundamentally from hyperthermia as it involves an active upward resetting of the hypothalamic set-point. This article presents a detailed scientific overview of the pathogenetic mechanisms underlying pyrogen-induced thermoregulatory shift, the cellular-molecular pathways of signal transduction across the blood-brain barrier, the distinct clinical-pathophysiological stages of fever, and its systemic impact on metabolism and immune responsiveness.

Keywords: Fever; Pyrexia; Pyrogens; Thermoregulation; Hypothalamic set-point; Blood-brain barrier; Pathophysiology; Immune response.

Introduction. Thermoregulation is a critical homeostatic mechanism that maintains core body temperature within a narrow physiological range despite fluctuating environmental conditions [3, 7]. When host defense mechanisms are triggered by infectious or non-infectious insults, the central thermoregulatory machinery undergoes dynamic functional reorganization [9, 11]. Within pathomorphological and pathophysiological frameworks, **fever** is defined as an active, cytokine-mediated systemic reaction characterized by a temporary alteration of the hypothalamic "set-point" (*set-point shift*), resulting in regulated hyperthermia [4, 8]. Exogenous pyrogens, primarily microbial components such as lipopolysaccharides, stimulate host immune cells to synthesize endogenous pyrogenic cytokines [1, 10]. These circulating mediators signal the preoptic area of the anterior hypothalamus to activate heat-conservation and heat-production pathways, culminating in elevated core temperature and enhanced metabolic responsiveness [6, 13, 14].

1. Etiology and Classification of Pyrogens

The initiation of fever requires the interaction between exogenous triggers and endogenous immune-inflammatory pathways.

Key Categories of Pyrogenic Agents

1. **Exogenous Pyrogens:** Pathogen-associated molecular patterns (PAMPs), including bacterial endotoxins (lipopolysaccharide complexes of Gram-negative bacteria), peptidoglycans, exotoxins of Gram-positive bacteria, viral ribonucleic acids, and fungal cell wall components.
2. **Endogenous (Cytokine) Pyrogens:** Host-derived pyrogenic cytokines synthesized predominantly by activated monocytes, macrophages, dendritic cells, and endothelial cells. Key endogenous pyrogens include:

- Interleukin-1 (IL-1β\text{IL-1}\betaIL-1β)

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- Interleukin-6 (IL-6\text{IL-6}IL-6)
- Tumor Necrosis Factor-alpha (TNF−α\text{TNF}-\alphaTNF−α)
- Interferon-alpha and gamma (IFN−α\text{IFN}-\alphaIFN−α, IFN−γ\text{IFN}-\gammaIFN−γ)

3. **Non-Infectious Etiological Factors:** Tissue necrosis (myocardial infarction, crush syndrome), immune complex disorders, massive hemolysis, surgical trauma, and malignant neoplasia.

2. Central Pathogenetic Mechanisms and Hypothalamic Resetting

The transformation of peripheral inflammatory signals into central thermoregulatory responses involves specialized neuro-vascular interfaces.

Exogenous Pyrogens (LPS / PAMPs)
↓
Activation of Monocytes / Macrophages
↓
Release of Endogenous Pyrogens (IL-1β, IL-6, TNF-α)
↓
Organum Vasculosum of the Lamina Terminalis (OVLT)
↓
Induction of Cyclooxygenase-2 (COX-2)
↓
Synthesis of Prostaglandin E2 (PGE2)
↓
EP3 Receptors in Preoptic Area of Hypothalamus
↓
Upward Resetting of Thermoregulatory Set-Point

Molecular Signal Transduction

- **Organum Vasculosum of the Lamina Terminalis (OVLT):** Endogenous pyrogens travel through the bloodstream to the OVLT—a circumventricular organ lacking a tight blood-brain barrier.
- **Prostaglandin E2\text{E}_2E2 (PGE2\text{PGE}_2PGE2) Cascade:** Pyrogenic cytokines stimulate endothelial cells and perivascular microglial cells in the OVLT to upregulate Cyclooxygenase-2 (COX-2\text{COX-2}COX-2) and Membrane-bound Prostaglandin E Synthase-1 (mPGES-1\text{mPGES-1}mPGES-1).
- **Hypothalamic Action:** PGE2\text{PGE}_2PGE2 crosses into the preoptic area (POA\text{POA}POA) of the anterior hypothalamus and binds to EP3\text{EP}_3EP3 receptors on warm-sensitive neurons. This inhibits warm-sensitive neuronal firing while disinhibiting cold-sensitive neurons, effectively elevating the hypothalamic temperature set-point.

3. Stages of Fever (*Stadia Febris*)

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The clinical course of fever progresses through three distinct pathophysiological phases, each characterized by specific thermoregulatory balances.

1. *Stadium Incrementi* (Stage of Temperature Elevation)

- **Mechanisms:** Heat production (*thermogenesis*) significantly exceeds heat dissipation (*thermolysis*).
- **Clinical Manifestations:** Peripheral vasoconstriction leading to skin pallor and cold extremities, piloerection ("goosebumps"), and involuntary muscle contractions (chills/rigors) driven by shivering thermogenesis.

2. *Stadium Fastigii* (Stage of High Temperature / Plateau)

- **Mechanisms:** Heat production and heat loss reach a new equilibrium at the elevated hypothalamic set-point level.
- **Clinical Manifestations:** Cutaneous vasodilatation causes skin flushing and warmth. Shivering ceases, metabolic rate remains markedly elevated, and core body temperature stays elevated with minor fluctuations.

3. *Stadium Decrementi* (Stage of Temperature De-escalation)

- **Mechanisms:** The hypothalamic set-point returns to normal baseline due to pyrogen clearance or antipyretic action; heat loss exceeds heat production.
- **Clinical Manifestations:** Profuse sweating (*diaphoresis*), pronounced cutaneous vasodilation, hyperventilation, and gradual or rapid (critical/lytic) return of body temperature to physiological norms.

4. Comparative Analysis: Fever vs. Non-Pyrogenic Hyperthermia

Feature / Parameter	Fever (Pyrexia)	Non-Pyrogenic Hyperthermia
Hypothalamic Set-Point	Elevated (active resetting via PGE2)	Unchanged (normal physiological baseline)
Primary Mechanism	Regulated physiological response	Uncontrolled heat accumulation or failure of thermolysis
Antipyretic Responsiveness	Responsive (COX inhibitors like paracetamol/ibuprofen)	Non-responsive to antipyretics
Thermoregulatory Effector Function	Preserved and coordinated	Overwhelmed or impaired
Etiology	Infections, pyrogenic cytokines, inflammation	Heat stroke, malignant hyperthermia, endocrine crisis
Biological Role	Adaptive host defense mechanism	Purely pathological, life-threatening

Conclusion. Fever is a highly conserved, coordinated physiological response to inflammatory and infectious challenges. Unlike hyperthermia, fever represents a controlled resetting of the central thermoregulatory set-point mediated by the cytokine-COX-2\text{COX-2}COX-2-PGE2\text{PGE}_2PGE2 pathway. While moderate fever enhances immune effector functions—including leukocyte migration, phagocytosis, and interferon activity—excessive or prolonged hyperpyrexia increases metabolic demand and cardiac workload, necessitating targeted clinical evaluation and evidence-based management.

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