

# Veterinary Insights

## Pathogenesis of Fever

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### Key Points

- Elevated body temperature may be caused by fever or hyperthermia.
- Fever is the result of the host body's recognition of a foreign invader.
- A complex cascade of events occur centrally, leading to thermal conservation and an elevated hypothalamic set point.
- Main pathway to elevation of hypothalamic set point is through arachidonic acid conversion to prostaglandin E2 (PGE2) catalyzed by cyclooxygenase (COX).
- While fever has some benefits in response to infection, uncontrolled fever can have negative consequences.

### Defining Fever

Elevated core body temperature is a common clinical sign in horses. The two most frequent causes of elevated body temperature are hyperthermia and fever. Hyperthermia is the passive (external) or active (exercise) gain of heat in excess of the body's ability to dissipate the heat.<sup>1</sup> Hyperthermia does not result from a change in the hypothalamic set point and is non-responsive to anti-pyretics.<sup>2</sup> Fever (pyrexia) is defined as "a state of elevated core temperature, which is often, but not necessarily, part of the defensive response of multicellular organisms (hosts) to the invasion of live (microorganisms) or inanimate matter recognized as pathogenic or alien by the host."<sup>3</sup> Pyrexia is the body's endogenous response to infectious, inflammatory, and other processes which trigger the release of cytokines and pyrogens, proteins released from viruses, bacteria, and the body's own cells which lead to a rise in body temperature.<sup>4</sup> These mediators initiate a cascade of events targeting the hypothalamus, elevating the hypothalamic set point, and producing pyrexia.<sup>2</sup>

### The Febrile Response

Many substances, both microbial and non-microbial, can elicit the febrile response. Most commonly, these are bacteria and viruses which initiate the cascade of events leading to fever, but fungi, drugs, and antigens can act as exogenous pyrogens. Neoplastic cells and host derived antigen-antibody complexes are examples of endogenous pyrogens.<sup>1</sup> Neither exogenous nor endogenous pyrogens themselves directly act upon the hypothalamus to cause fever. Pyrogens trigger a complex cascade of events which elevate the centrally

located hypothalamic set point. As they are the most common exogenous pyrogens, we will use an infectious microorganism as the example in illustrating the pathogenesis of fever.

## Response to Pyrogens

An infectious microorganism which evades the host's initial defensive barriers — skin, mucous membranes, and resident microbial populations — will encounter cells of the immune system, tissue macrophages, monocytes, and neutrophils upon entering the blood stream. Macrophages express receptors for many microbial constituents, binding to these receptors stimulates the release of a collection of mediators contributing to a local inflammatory response.<sup>1</sup> The microorganism may also be transported to the liver where Kupffer cells are activated and release mediators. Among the mediators released are the two proximate mediators of fever, tissue necrosis factor-alpha (TNF- $\alpha$ ) and interleukin 1-beta (IL-1 $\beta$ ) — as well as interferons (IFN) and IL-6.<sup>1,2,4</sup>

## Mediators of Fever and Therapeutic Targets

Fever is a clinical sign mediated by cytokines, short polypeptide segments involved with cell signaling.<sup>5</sup> Transported via the bloodstream, the cytokines reach the preoptic-anterior hypothalamus (POA), binding to specific receptors on neurons and endothelial cells in the area proximal to the Organum Vasculosum Lamina Terminalis (OVLT).<sup>2,5</sup> Mediator interaction with cells of the POA results in increased central production of PGE2 via upregulation of phospholipase A2, creating the arachidonic acid substrate for the upregulated cyclooxygenase (COX) pathway to convert to PGE2.<sup>2,5</sup> There are three COX isoenzymes: COX-1 is substantive and generally involved with cytoprotective functions; COX-2 is inducible and responsible in large part for the inflammatory response; and COX-3, a variant of COX-1, is largely centrally located and responsible for analgesic and anti-pyretic responses.<sup>6,7</sup> COX inhibitors, either selective or non-selective, are frequently administered as antipyretics. Pyrogen binding at the POA also allows movement of PGE2, produced by peripheral endothelial cells, across the blood-brain barrier, increasing central levels.<sup>2</sup> PGE2 binds to E type prostaglandin receptors (EP receptors), mainly EP3 subtype, on the hypothalamus resulting in neuronal signaling, initiating a cascade of reactions resulting in elevation of the set point in the hypothalamic thermoregulatory center, heat conservation, and heat generation.<sup>2,8</sup>

## Summary

Fever has been demonstrated to have beneficial effects for survival and has been preserved evolutionarily for over 600 million years across widely diverse animal groups, from vertebrates to insects.<sup>9,10</sup> However, fever is not always beneficial, as demonstrated in cases of extreme inflammation or uncontrolled fevers in some cases of sepsis or neurologic injuries.<sup>9</sup> While pyrexia has physiologic benefits, it must be remembered that the cytokines acting as pyrogens are also the mediators of the septic process.<sup>11</sup> Thus, unchecked, pyrogenic cytokines have the potential to be harmful as well as beneficial during processes which result in the body generating fever.<sup>11</sup> There are metabolic costs associated with fever — in humans, approximately 10% for each degree (°C) increased body temperature.<sup>12</sup> In veterinary species, particularly the horse, fever and the associated anorexia/decreased water intake and elevated mediators of the septic process, may lead to muscle wasting and weight loss and potentially life-threatening sequelae to the underlying cause of the fever.<sup>2,13,14</sup>

## References

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