THE MECHANISMS OF FEVER: IMPLICATIONS FOR CLINICAL AND BASIC SCIENCE

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There is considerable evidence that fever evolved as a non-specific host defence response to infection. Although physicians often treat "fever" as though it was a harmful manifestation of disease, this seems to be becoming less common. Within the past 30 years it has become increasingly clearer that during infection a fever is a highly regulated process, with both endogenous pyrogens and endogenous antipyretics being generated. Thus fever is a balance between fever-inducing agents (pyrogens) and fever suppressing factors or cryogens (Table). With some exceptions, the pyrogenic factors and processes tend to be pro-inflammatory, while the cryogenic branch is primarily antiinflammatory.

Pyrogens	**Cryogens**
Interleukin-1	Arginine Vasopressin
Interleukin-6	Alpha Melanocyte Stimulating Hormone
Interferons	Glucocorticoids
Tumor necrosis factor	Tumor necrosis factor
Macrophage Inflammatory Factor	Interleukin-10
Prostaglandin E_2	Epoxyeicosatrienoic acids (EETs)

Although the metabolism of arachidonic acid (AA) is generally thought to be pro-inflammatory, primarily via the production of prostaglandins and leukotrienes, there is now compelling evidence that metabolism of AA via cytochrome P-450/epoxygenases produces both antipyresis and reduction of inflammation. Four kinds of data demonstrate that P-450 is involved in antipyresis/anti-inflammation: (i) treatment with inhibitors of P-450 causes larger fever (Nakashima *et al.*, 1996; Kozak *et al.*, 1998); (ii) inducers of P-450 prevent fever (Kozak *et al.*, 2000) and suppress lung inflammation due to intratracheal instillation of LPS (manuscript submitted); (iii) P-450 epoxygenase-derived eicosanoids (EETs) suppress fever (Kozak *et al.*, 2000); (iv) EETs suppress expression of adhesion molecules on endothelial cells (Node *et al.*, 1999). We believe that investigating fever and endogenous antipyresis will provide clinicians with additional mechanisms to modulate inflammation.

Kozak, W., Archuleta, I., Mayfield, K.P., Kozak, A., Rudolph, K., Kluger, M.J., 1998. Inhibitors of alternative pathways of arachidonate metabolism differentially affect fever in mice. *Am. J. Physiol.* 275, R1031-R1040.

Kozak, W., Kluger, M.J., Kozak, A., Wachulec, M., Dokladny, K., 2000. Role of cytochrome P-450 in endogenous antipyresis. *Am. J. Physiol.* 279:R455-R460.

Nakashima, T., Harada, Y., Miyata, S. Kiyohara, T. 1996. Inhibitors of cytochrome P-450 augment fever induced by interleukin-1. *Am. J. Physiol.* 271:R1274-R1279.

Node, K., Huo, Y., Ruan, X., Yang, B., Spiecker, M., Ley, K., Zeldin, D.C., Liao, J.K., 1999. Anti-inflammatory properties of cytochrome P450 epoxygenase-derived eicosanoids. *Science* 285, 1276-1279.

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