Imagine you were hit by the flu. Taking a look at the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology in this unpleasant situation will certainly not prevent you from getting a fever. However, by doing so you can learn at least some interesting news about the mechanisms that control your body temperature.

Bacterial lipopolysaccharides (LPS) induce fever that is mediated by pyrogenic cytokines, such as IL-1β. Recent findings indicate that IL-1β may communicate to the brain via a neural pathway involving activation of vagal afferents in addition to blood-borne routes. Thus subdiaphragmatic vagotomy completely blocked the fever response to intraperitoneal injection of IL-1β in rats, and this effect was highest at low cytokine doses (8). In contrast, vagotomy failed to inhibit intravenous leptom-induced IL-1β expression in the hypotalamus, suggesting that circulating leptin directly acts in the brain independently of afferent vagus nerve input originating from the subdiaphragmatic organs (10). A normal febrile response to pyrogenic stimuli at thermoneutrality was also seen in obese Zucker rats, which have a so-called fatty mutation in the leptin receptor gene (13). Therefore, fatty mutation does not interrupt febrigenic signaling from the periphery to the brain.

There are also “good” cytokines that may counteract an increase of the body core temperature. For example, the febrile response induced by IL-1β was attenuated by pretreatment either with IL-10 or IL-6, which inhibited IL-1β production in the hypothalamus and brain stem (18). Falling asleep is probably the most convenient way to cope with a fever. As demonstrated in two elegant studies, intracerebroventricular injection of IL-2, IL-15, and IL-18 enhanced non-rapid eye movement sleep in rabbits and rats, indicating a role for cytokines in the sleep response to infection (16, 17). The potency of cytokines to induce fever is normally controlled by binding to specific cytokine carriers such as α2-macroglobulin (α2M). It was shown in a recent paper that LPS-induced fever is attenuated in α2M-deficient mice compared with wild-type animals (7). At 1.5 h after injection of LPS, the plasma concentration of TNF-α, but not of IL-1β or IL-6, was significantly lower in α2M−/− than in normal mice. These findings suggest that a putative mechanism of α2M involvement in fever is through the inhibition of TNF-α clearance (7).

In addition to enhanced cytokine release, the PGE2 system is another important downstream mediator of fever and inflammation. Recent experimental evidence indicates that activation of PGE2 by bacterial LPS involves both differential transcriptional upregulation of PGE2 synthesizing enzymes (12) and downregulation of PGE2 carriers and catabolizing enzymes in various tissues (14). Among the most remarkable changes in LPS-injected rats was a decrease in the expression of hepatic and pulmonary 15-hydroxy-PG-dehydrogenase and increased microsomal PGE synthase as well as secretory phospholipase A2-II-A mRNA in the hypothalamus and liver (14). These enzymes are therefore attractive targets for anti-inflammatory therapy. It seems that the PGE2 pathway is also responsible for the attenuation of fever in pregnant animals. Thus LPS-induced PGE2 production was suppressed in the brain of near-term pregnant rats, and this effect was correlated with blunted cyclooxygenase-2 induction in brain endothelial cells of these animals (11, 19). The sensitivity to PGE2 was also maintained during hibernation as demonstrated by the finding that intracerebrovascular infusion of PGE2 in golden-mantled ground squirrels provoked arousal from hibernation and induced fever (21). It is believed that periodic arousals may activate a dormant immune system, which can then combat pathogens that may have been introduced immediately before or during hibernation (21).

The central heme oxygenase (HO) pathway was reported to play an important role in the genesis of LPS-induced fever. Novel findings suggest that among the HO products involved, i.e., biliverdine, free iron, or carbon monoxide, CO acting via a soluble guanylate cyclase is the most likely candidate for LPS fever. This conclusion is based on the findings that intracerebroventricular application of biliverdine or iron salts as well as treatment with the iron chelator deferoxamine elicited no change in basal body core temperature (23). However, heme-induced pyresis was completely prevented by inhibition of the soluble guanylate cyclase pathway, which is normally activated by CO (23). In an effort to study the role of the nitric oxide (NO) system in the regulation of body core temperature, the NO synthase inhibitor Nω-monomethyl-arginine (l-NMMA) was injected into the anteroventral preoptic region (AVPO) of rats. l-NMMA did not affect the basal

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body core temperature but enhanced the early stage of LPS fever, indicating that NO plays an antipyretic role in the AVPO (22). It seems that peripherally generated NO contributes to the genesis of fever, whereas brain NO may act as an endogenous antipyretic factor, at least in response to systemic inflammation (22).

The role of the liver in modulating the fever response to pyrogenic stimuli is highlighted in two studies, which appeared in the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology. One of these studies shows that selective inhibition of hepatic protein synthesis with D-galactosamine (D-gal) blunted the febrile response to LPS in both control animals and heat-conditioned rats (2). Intraportal injection of D-gal also abolished pyrogenic tolerance to repeated treatment with muramyl dipeptide, suggesting that hepatic function may be important not only for the development of tolerance to endotoxin (20) but also to other pyrogenic stimuli (3). Although muramyl peptide and LPS are T cell-independent stimuli of the immune system, the staphylococcal enterotoxin B was used to assess the role of the T cell system in eliciting an immune response. Intraportal injection of staphylococcal enterotoxin B resulted in a significant rise of body temperature in rats and elevation of plasma corticosterone as well as c-Fos expression in parvocellular neurons within the paraventricular nucleus of the hypothalamus (6). These observations support the idea that T cell-dependent immune stimuli activate brain pathways mediating host-defense responses such as fever and neuroendocrine changes (6).

As outlined in several contributions, the fever response to pyrogenic signals is not uniform but depends on various external and endogenous conditions. For example, alcohol consumption was reported to aggragate alterations in body temperature due to shift work, jet lag, and aging in humans (1). Furthermore, rats suffering from repeated restraint (9) or physical stress (15) showed enhanced response to LPS both in terms of body core temperature as well as hypothalamic-pituitary-adrenal function. Another interesting aspect refers to the fact that LPS-induced fever is related to behavioral thermoregulation in young and old rats. For example, young rats that were injected with LPS reproducibly developed fever at an ambient temperature of 23°C. On the contrary, the old animals showed significantly warmer positions in a thermal gradient than did the young rats and only then became febrile (4). These observations suggest that LPS may increase the thermal set point in old rats, which can develop fever only at higher ambient temperature than the young animals (4).

In the end, the expanding knowledge about the mechanisms of body temperature control will hopefully enable researchers to develop strategies of pharmacologically modulating the fever response to various pyrogens.

REFERENCES

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