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Endothelin—an emerging role in proinflammatory pathways in brain

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As one of the most common symptoms of infectious disease, fever has been intensively studied over the past 75 years. An understanding of the cascade of events leading from bacterial invasion of the body to the development of an elevated body temperature began to emerge in the 1970s and early 1980s. A mechanism was envisioned whereby the active component of bacterial cell walls, LPS, interacts with immune cells that produce a variety of cytokines, in particular, IL-1β, IL-6, and TNF-α. Whereas the means by which the cytokines signal to the brain may vary according to both the quantity of cytokines and whether they are localized to a peripheral site (i.e., an inflammatory locus) or are found in the circulation (as in endotoxemia), it was widely accepted that the synthesis of PGs (in particular, PGs of the E series) is initiated within the brain; these PGs then act on neurons within the anterior hypothalamic/preoptic area to activate heat conservation and production and limit heat loss, such that body temperature is elevated. This scenario fits in well with the known actions of antipyretic drugs and with the temporal sequence of the febrile process.

Whereas this basic understanding of the febrile process remains unchallenged, it is now apparent that fever is much more complex. In association with the production of a number of proinflammatory molecules, there is now known to be concurrent synthesis and actions of a number of other pro- and anti-inflammatory molecules, including anti-inflammatory cytokines (2, 16), hormones (14), and neurotransmitters (1, 23). Even the proinflammatory side of the equation has become much more complex; peripherally generated pyrogenic products may include other cytokines (4), leptin (17), platelet activating factor (11), and complement (24), as well as inflammatory mediators that do not activate the PG cascade (8). A number of other peptidergic molecules, such as corticotrophin-releasing hormone (23), vasopressin (3), and ANG II (27) have been implicated in the febrile process. Both pro- and anti-inflammatory cytokines, which are synthesized within the brain, appear to be important intermediaries (12). In short, the situation is not nearly as clear as it once was.

A recent addition to the roster of inflammatory molecules is endothelin (ET). ET was discovered in 1988 and appears as three different isoforms (ET-1, -2, -3) and acts on ETA or ETB receptors (10, 18, 28). The peptides are synthesized in vascular endothelial cells (thus the name) and were originally characterized for their intense vasoconstrictor activity on vascular smooth muscle. However, like many such molecules, they have now been found to be synthesized in a variety of tissues and to have receptor-mediated actions on many different tissues throughout the body.

Of relevance to this editorial focus is the report from Souza and colleagues (6) at the Universidade de São Paulo who reported that ET-1 not only caused fever after intracerebroventricular (ICV) injection into rats, but that an ET receptor antagonist attenuated fevers due to systemically administered LPS and IL-1β, as well as to ICV IL-1β or TNF-α. What was particularly interesting about this observation was that the pyrogenic response to ET-1 was not modified by the cyclooxygenase (COX) inhibitor indomethacin, suggesting that PGs were not involved. A subsequent paper (7) further investigated the involvement of PGs with the use of specific COX-2 inhibitors, but the data are somewhat confusing. The COX-2 inhibitor celecoxib reduced cerebrospinal fluid PG induced by either LPS or ICV ET-1, but the fever induced by ET-1 was not attenuated, at least at the doses effective in reducing the PG levels. On the basis of these results, the authors again suggested that there may be ET-dependent febrile actions independent of PGs.

In this issue of the journal, these authors (5) again attempt to unravel the role of ET-1 and its receptors in fever, in particular, addressing its possible involvement in non-PG-dependent fevers. With the use of various selective receptor antagonists, they have concluded that several parallel pathways within the brain are activated by peripherally administered LPS, with ET-1 being an intermediary in a pathway involving sequential release/action of a still uncharacterized factor called preformed pyrogenic factor, corticotrophin-releasing hormone, ET-1 (via ETA receptors), and finally IL-1β. This pathway is independent of, but parallel to, other pathways also involving ILs, TNF-α, PGE₂, or PGF₂α. (See Fig. 7 of Ref. 5 for a schematic of these postulated pathways.)

These interesting findings raise numerous questions and avenues for further investigation. Key questions, yet undressed, arise from these findings. Under what conditions do each of these pathways contribute to fever? Are they activated in response to different doses of LPS or in response to different signaling pathways to the brain? Are these different pathways activated at different times of the febrile process? Is it interesting that ICV ET-1 fevers have an onset latency of 2 h, with a peak around 4–6 h. LPS-induced fevers consist of at least three phases (21), most likely due to several waves of pyrogenic and antipyretic molecules. On the basis of its long latency of action, ET-1 may be a candidate for the latter phases of the fever.

Non-PG-dependent fevers remain poorly understood, and the mechanisms of their development remain obscure. At least in mice, all evidence indicates that absence of either specific PG receptors (20, 25) or COX-2 (15) abolishes fever to LPS. If a similar situation were to exist in rats, one might ask why a non-PG-dependent pathway, possibly involving ET-1, would not support a fever in a PG-deficient rodent?
As a peptide molecule, it is unlikely that ET-1 can enter the brain from the periphery. The present study thus appears to implicate brain ET-1 as a mediator of the febrile process. This is quite possible because ETs are synthesized in the brain, largely in astrocytes (9), and their receptors are widely distributed throughout neuronal tissue (13). Nonetheless, vascular endothelial cells produce ET-1 in response to LPS (22), and peripheral administration of LPS, at least in large doses, is associated with measurable levels of ET-1 in the plasma (19). A site where there are numerous ET$_B$ receptors is the subfornical organ (9), which is outside the blood-brain barrier, and the action of systemic ET-1 on hypothalamic neuronal activity has been shown to be dependent on subfornical organ integrity (26). Because this structure is also accessible from the cerebral ventricles, one cannot eliminate the possibility that the effects on body temperature due to ICV administration of ET-1 or of receptor antagonists, reflect the action of circulating ET-1 rather than that which is centrally produced.

Finally, the use of ICV injections to investigate neurotransmitter pathways in the brain provides a useful first approach to implicating this peptide in fever. Future studies must address the anatomical specificity of the various parallel pathways. It would also be useful to investigate LPS fever in ET-1 or ET receptor knockout mice (13). Whatever the outcome of such studies, it is apparent from the present study (5) that ET has emerged as a significant player in the inflammatory process. Thus like a number of other peptides, a former “cardiovascular” peptide has an action on a distinctly different autonomic function, in this case, fever.

ACKNOWLEDGMENTS

Work in the author’s lab is supported by the Canadian Institutes of Health Research and a Medical Scientist Award from the Alberta Heritage Foundation for Medical Research.

REFERENCES