Febrile nonresponsiveness of vagotomized animals: is it due to endotoxin translocation from the gut and tolerance?

To the Editor: In their recent article, Scammell and colleagues (5) discuss afferent signals that drive preoptic prostaglandin E2 synthesis and fever after intravenous injection of lipopolysaccharide (LPS). The authors examine the concept of these signals being carried to the brain by the vagus nerve and take a closer look at the neuroanatomic sites of prostaglandin synthesis that produce fever remain unknown. With the use of a novel microinjection technique, we injected the cyclooxygenase inhibitor ketorolac into the preoptic area (POA) to determine which preoptic regions produce the prostaglandins required for fever. Initial experiments demonstrated that intravenous ketorolac blocked the fever normally produced by lipopolysaccharide (LPS) 5 µg/kg iv. Microinjection of ketorolac into the POA had no effect on body temperature, and injection of artificial cerebrospinal fluid into the POA did not alter LPS fever. Injection of ketorolac into the anteroventral POA markedly decreased the fever produced by LPS, compared with injections into more rostral, caudal, or dorsal locations. These observations indicate that prostaglandin synthesis in the anteroventral preoptic region is necessary for the production of fever.

Scammell, Thomas E., John D. Griffin, Joel K. Elmquist, and Clifford B. Saper. Microinjection of a cyclooxygenase inhibitor ketorolac into the anteroventral preoptic region attenuates LPS fever. Am. J. Physiol. 274 (Regulatory Integrative Comp. Physiol. 43): R933–R935, 1998.—Considerable evidence supports the role of prostaglandins in fever production, but the neuroanatomic sites of prostaglandin synthesis that produce fever remain unknown. With the use of a novel microinjection technique, we injected the cyclooxygenase inhibitor ketorolac into the preoptic area (POA) to determine which preoptic regions produce the prostaglandins required for fever. Initial experiments demonstrated that intravenous ketorolac blocked the fever normally produced by lipopolysaccharide (LPS) 5 µg/kg iv. Microinjection of ketorolac into the POA had no effect on body temperature, and injection of artificial cerebrospinal fluid into the POA did not alter LPS fever. Injection of ketorolac into the anteroventral POA markedly decreased the fever produced by LPS, compared with injections into more rostral, caudal, or dorsal locations. These observations indicate that prostaglandin synthesis in the anteroventral preoptic region is necessary for the production of fever.

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To the Editor: In our recent article (9), we described the attenuation of lipopolysaccharide (LPS) fever by inhibition of prostaglandin synthesis in the preoptic area. We and others have proposed that LPS and circulating cytokines may activate perivascular and meningeal cells, which then release prostaglandin E2 into the preoptic area to initiate fever. As we, Romanovsky, and others have previously suggested (4, 6, 8), pyrogens may signal the brain through multiple routes, depending on the site and intensity of inflammation. It is possible that the hepatic branch of the vagus may be one of the most sensitive signaling pathways. However, LPS-induced activation of autonomic regulatory neurons as indicated by expression of c-fos and corticotropin-releasing factor (CRF) is not blocked by vagotomy (5).

As we, Romanovsky, and others have previously suggested (4, 6, 8), pyrogens may signal the brain through multiple routes, depending on the site and intensity of inflammation. It is possible that the hepatic branch of the vagus may be one of the most sensitive signaling pathways. However, LPS-induced activation of autonomic regulatory neurons as indicated by expression of c-fos and CRF after vagotomy indicates that nonvagal, vascular pathways also play an essential role in the febrile response. Future experiments may help clarify the relative contributions and interactions of these vagal and vascular mechanisms.

REFERENCES


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