THE HUMORAL MECHANISM THAT ACTIVATES BRAIN PROSTAGLANDIN E_2 BIOSYNTHESIS DURING FEVER

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Fever is mediated through production of prostaglandin E_2 (PGE_2) in the brain. To understand where and how PGE_2 is produced in the brain, we have been studying expressions of enzymes responsible for PGE_2 biosynthesis in the rat brain and its relevance to fever. In our typical experiment, rats were challenged with lipopolysaccharide (LPS, 0.1-0.4 mg/kg, i.p.). Five hours after the injection, their brain and cerebrospinal fluid were sampled for histological analysis and PGE_2 assay, respectively, under diethyl ether or pentobarbital anaesthesia (5 mg/kg). In some cases, rats were pretreated with NS-398 (4 mg/kg, i.p.), an inhibitor of cyclooxygenase-2 (COX-2), prior to the LPS injection. The results were summarized as follows: (1) COX-2, an inducible-type enzyme converting arachidonic acid to PGH_2, was induced in brain endothelial cells in response to LPS (Matsumura *et al.*, 1998); (2) COX-2 expression was correlated with fever in terms of timing and magnitude (Cao *et al.*, 1997); (3) Inhibition of COX-2 activity suppressed fever (Cao *et al.*, 1997); (4) Microsomal-type PGE synthase (mPGES), another key enzyme that converts PGH_2 to PGE_2, was also induced in brain endothelial cells after LPS challenge; (5) mPGES was colocalized with COX-2 in the perinuclear region of the endothelial cells (Yamagata *et al.*, 2001); (6) Inhibition of COX-2 activity suppressed PGE_2 level in the brain; (7) Endothelial cells are the only cell group that expresses both COX-2 and mPGES in the brain; (8) Cytokine receptors are expressed in brain endothelial cells; (9) COX-2 induction and PGE_2 elevation were not suppressed by bilateral vagotomy at the cervical level indicating that these responses are not vagally-mediated; and (10) Even under untreated conditions, low amounts of COX-2 and mPGES have been already expressed in brain endothelial cells. These results strongly suggest that circulating LPS and/or cytokines act on brain endothelial cells, which, in turn, produce PGE_2 through inductions of COX-2 and mPGES. This seems to represent one of the humoral mechanisms of immune-brain communication that leads animals to fever.

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