Prostaglandins and sepsis: still a fascinating topic despite almost 40 years of research

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NORTHOVER AND SUBRAMANIAN (31) reported in 1962 that treating dogs with aspirin, a prototypical nonsteroidal anti-inflammatory drug (NSAID), ameliorated the development of arterial hypotension after the injection of lipopolysaccharide (LPS). Subsequent to this early report, many other investigators confirmed that treatment with aspirin or other NSAIDs improved hemodynamic parameters, organ system function, and even survival in various animal models of endotoxemia (3, 12, 14, 15) or sepsis (7, 11). The primary pharmacological action of NSAIDs, of course, is to decrease the formation of prostaglandins (PGs) and thromboxanes (TXs) by inhibiting cyclooxygenase (COX), a key enzyme in the biochemical pathway leading to the formation of these potent mediators (46). Accordingly, products of the COX pathway, sometimes referred to as “prostanoids,” have been implicated in the pathogenesis of the deleterious systemic consequences of serious infection and/or endotoxemia. Other lines of evidence also support this concept. For example, circulating concentrations of 6-keto-PGF1α (prostacyclin metabolite) and TXB2 (TXA2 metabolite) increase after administration of LPS to experimental animals (3, 12, 14, 15). Furthermore, blocking prostanoid production by nonpharmacological means, such as by creating a state of essential fatty acid deficiency, improves survival after administration of a lethal dose of LPS (3). In addition, the toxic effects of tumor necrosis factor (TNF), thought to be one of the primary cytokines responsible for LPS-induced lethality, can be ameliorated by treating mice or rats with NSAIDs such as indomethacin or ibuprofen (13, 23).

We now recognize that there are two COX isoforms, COX-1 and COX-2 (28). COX-1 is constitutively expressed in most tissues (5, 39), whereas COX-2 expression can be induced by various proinflammatory substances, including LPS, TNF, and interleukin (IL)-1, in a wide variety of cell types (6, 17, 22, 27, 30, 32–34). Accumulating data suggest that the inhibition of COX-2 is actually a key mechanism whereby NSAIDs diminish inflammation (18, 26). Because some of the side effects of treatment with NSAIDs, such as gastric mucosal irritation, are thought to be caused by inhibition of COX-1, isoform-selective COX-2 inhibitors have been developed and introduced into clinical practice (4).

Although COX-2 expression can be increased by proinflammatory cytokines, the predominant effects of PGE2 tend to be anti-inflammatory. Thus this mediator has been shown to downregulate a variety of immunologic responses, including the production of IL-2 by T cells (2, 19), the activation and proliferation of B cells (21, 44), the expression of Ia on macrophages (40), and the phagocytosis of particles by macrophages (1). PGE2 also inhibits a number of neutrophil functions, including enzyme release, chemotaxis, and oxygen radical production (10, 16). Moreover, in a form of negative feedback, E series PGs downregulate the release of TNF from various inflammatory cells (25). PG-mediated downregulation of TNF expression, which occurs at the gene level (20, 24), depends on release of the counterregulatory cytokine IL-10 (42). Interruption of this feedback loop with NSAIDs has been shown to increase cytokine (TNF, IL-6, or IL-8) release by stimulated mononuclear cells in vitro (8, 9, 45), in animals challenged with LPS (36, 38), and in human volunteers infused with small doses of LPS (29, 41).

Important new information regarding the role of prostanoids and COX-2 in the pathophysiology of endotoxemia and sepsis is provided in the report by Reddy et al. (35) in this issue of the American Journal of Physiology—Lung Cellular and Molecular Physiology. These investigators evaluated the effect of pretreatment with NS-398, a highly selective COX-2 inhibitor, on survival and inflammatory mediator production in two models of sepsis in mice (LPS challenge and peritonitis induced by cecal ligation and puncture). Pretreatment with NS-398 failed to improve long-term survival in either of the models studied, although in the endotoxemia model, administration of the COX-2 inhibitor had a modest salutary effect on early mortality. In addition, although treatment with NS-398...
blocked LPS-induced increases in the circulating levels of immunoreactive PGE$_2$, injection of the COX-2 inhibitor did not modulate plasma concentrations of TNF or the C-X-C chemokine KC.

Thus, in marked contrast to results that have been previously reported in studies with isoform nonselective COX inhibitors (14, 15), the data obtained by Reddy et al. (35) indicate that pharmacological inhibition of COX-2 has only very modest effects on the outcome in experimental sepsis or endotoxemia. Because these results are discrepant with respect to the findings that have been obtained with isoform nonselective agents, it is regrettable that Reddy et al. did not include a “positive control” arm in their studies to evaluate the effects of treatment with an agent such as indomethacin or ibuprofen in their own laboratory’s models of sepsis. Certainly, the results reported in this issue of the American Journal of Physiology-Lung Cellular and Molecular Physiology prompt one to wonder whether similar findings would be obtained in a study with mice with a targeted disruption of the COX-2 gene.

The results reported by Reddy et al. (35) are also somewhat discrepant with respect to some earlier findings from studies that used NS-398 to block COX-2 in models of experimental infection. For example, Shoup et al. (37) reported that twice daily treatment with NS-398 improved long-term survival (from 0 to 45.5%) in mice subjected to a 15% cutaneous scalp burn followed by infection with viable Pseudomonas aerugi- nosa. Similarly, Strong et al. (43) showed that administration of NS-398 for 24 h after trauma (femur fracture) improved survival when mice were subjected to cecal ligation and puncture 7 days later. It is noteworthy that NS-398 demonstrated protective effects in two models of sepsis characterized by infection in the setting of trauma-induced immunosuppression, whereas the drug was largely ineffective when sepsis was induced in immunocompetent animals. Taken together, these observations might suggest that COX-2-derived prosta-
noids (particularly PGE$_2$) contribute to immunosuppression induced by trauma but are relatively unimportant in the pathogenesis of sepsis.

The results obtained by Reddy et al. (35) also suggest that the COX-1 pathway (i.e., the pathway that is not generally regarded as the one involved in inflammation) is actually more important than the COX-2 pathway with respect to prostanoid-induced pathophysiological effects in endotoxemia and sepsis. Clearly, despite almost 40 years of investigation, we still have a great deal to learn regarding the role of the prostanoids in the pathogenesis of sepsis and septic shock.

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