Arthritis Rheum. 2001 Sep;44(9):2078-83.

Interleukin-1, tumor necrosis factor alpha, and interleukin-17 synergistically up-regulate nitric oxide and prostaglandin E2 production in explants of human osteoarthritic knee menisci.

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Abstract

OBJECTIVE:

In osteoarthritis (OA), a combination of biochemical and biomechanical factors may damage both menisci and articular cartilage. Nitric oxide (NO) and prostaglandin E2 (PGE2) have been implicated as mediators of inflammation in OA. The goals of this study were to determine if menisci from patients with OA produce NO and PGE2, and if the proinflammatory cytokines interleukin-1beta (IL-1beta), tumor necrosis factor a (TNFalpha), and IL-17 augment NO and PGE2 production by these tissues.

METHODS:

Menisci were obtained from 17 patients (age 47-75 years) undergoing total knee replacement for OA. Tissue explants were cultured alone or with IL-1beta, IL-17, or TNFalpha, and the release of NO and PGE2 from the tissue as well as the presence of type 2 nitric oxide synthase (NOS2) and cyclooxygenase 2 (COX-2) antigens were measured.

RESULTS:

All menisci constitutively produced NO, and significant increases in NO production were observed in the presence of IL-1beta, TNFalpha, or IL-17 ($P < 0.05$). The combination of IL-17 and TNFalpha significantly increased NO production compared with either cytokine alone. Basal and cytokine-stimulated NO synthesis was inhibited by the NOS inhibitors NG-monomethyl-L-arginine or N-3-aminoethylbenzylacetamidine (1400W). IL-1beta significantly increased PGE2 production. The combination of IL-1beta and TNFalpha had an additive effect on PGE2 production, while addition of IL-17 to TNFalpha or IL-1beta synergistically enhanced PGE2 production. Inhibition of NO production by 1400W significantly increased IL-1beta-stimulated PGE2 production, and inhibition of PGE2 production by the COX-2 inhibitor N-[2-(cyclohexyloxy)-4-nitrophenyl]-methanesulfonamide significantly increased IL-17-stimulated NO production.

CONCLUSION:

Menisci from humans with OA spontaneously produced NO and PGE2 in a manner that was synergistically or additively augmented by cytokines. NO and PGE2 exhibited reciprocal regulatory effects on one another, suggesting that pharmaceutical agents designed to inhibit NOS2 or COX-2 production may in fact be influencing both pathways.