EICOSANOID PRODUCTION DURING THE DEVELOPMENT OF ANTIGEN-INDUCED CHRONIC ARTHRITIS

B. Henderson*, G.A. Higgs, K.E. Jackson and J.A. Salmon, Department of Prostaglandin Research, Wellcome Research Laboratories, Langley Court, Beckenham, Kent BR3 3BS.

Prostaglandin E_2 (PGE_2) and leukotriene B_4 (LTB_4) are found in the synovial fluid of patients with established rheumatoid arthritis and it is likely that these eicosanoids contribute to the pathology of this disease.

We have now investigated the synthesis of eicosanoids following the induction of immune arthritis in rabbits (Dumonde & Glynn, 1962). New Zealand White or Old English rabbits were sensitized to ovalbumin and challenged by injection of antigen into the knee joint of one hind limb. The contralateral joint received a similar injection of saline. Animals were killed 1-16 days after challenge and joint fluids were collected from both knees by washing the joint space with saline. Samples of synovial lining were removed from each joint and maintained for 24h in non-proliferative organ culture (Poulter et al., 1970). The concentrations of PGE_2, LTB_4, 6-keto-$PGF_{1\alpha}$ and thromboxane B_2 (TXB_2) in joint washes and organ culture fluids were determined by specific radioimmunoassays (Salmon et al., 1983).

Antigen-challenged joints developed an arthritic response which was sustained until the animals were killed and did not occur in the control joints. Joint fluids collected 24h after induction of arthritis contained 10.5 ± 2.5 ng/ml immunoreactive PGE_2 (mean ± s.e. mean) and 0.23 ± 0.16 ng/ml immunoreactive LTB_4. After 12-16 days PGE_2 concentrations in arthritic joint fluids had fallen to about 0.5 ng/ml and LTB_4 was undetectable (<0.05 ng/ml). At 24h control joint fluids contained 0.4 ± 0.2 ng/ml PGE_2 but no detectable LTB_4. From 5-16 days there was no detectable PGE_2 or LTB_4 in the control joint fluids. The concentrations of PGE_2 found in the joint washes from arthritic joints were similar to those reported by Blackham et al. (1974).

Prostaglandin production in cultures of synovial explants from arthritic joints increased progressively from 1-16 days reaching peaks of 14.2 ± 3.6 ng PGE_2 per mg wet weight of tissue and 1.8 ± 0.38 ng/mg immunoreactive 6-keto-$PGF_{1\alpha}$. There was a lower production of immunoreactive TXB_2 (0.35 ± 0.021 ng/mg) and LTB_4 (0.0091 ± 0.0023 ng/mg). Interestingly, in tissues taken 24h after antigen challenge, the production of PGE_2 and 6-keto-$PGF_{1\alpha}$ by control tissues was significantly higher than in arthritic tissues. In explants taken at 5-16 days, however, PGE_2 and 6-keto-$PGF_{1\alpha}$ synthesis in control tissues declined to approximately 20% of arthritic values. The synthesis of TXB_2 and LTB_4 by arthritic synovium was significantly greater than that of control tissues at all the sampling times.

These results show that in an experimental model of chronic arthritis the synovial lining has an elevated capacity for eicosanoid synthesis and that the development of the response is accompanied by the production of prostaglandins, thromboxanes and leukotrienes.

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