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Arthritogenic activity of interleukin 1

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Introduction

Interleukin 1 (IL-1) has been detected in the synovial fluid of patients with various erosive arthritides [1]. IL-1 also has many *in vitro* activities which suggest it may play a role in the cartilage and bone erosion that occur in chronically inflamed joints [2].

Therefore, in this study we have investigated the effect of intra-articular injections of human highly purified IL-1 on leukocyte infiltration into the joint fluid and on cartilage proteoglycan loss – a measure of cartilage degradation.

Materials and methods

1–20 units of human highly purified IL-1 (Genzyme), in 0.5 ml saline, were injected into the knee joints of groups of New Zealand white rabbits (2.5–3.0 kg) and the contralateral joint of each animal received vehicle alone. The animals were sacrificed 4 h to 3 days after injection and the joint diameters measured by calipers. The joints were washed with 1 ml sterile saline and the leukocytes separated from the joint fluid by centrifugation. The cell-free joint wash was stored at −20 °C and later assayed for prostaglandin E_2 (PGE_2) and leukotriene B_4 (LTB_4) by specific radioimmunoassay. Total and differential counts were performed on the leukocytes, after staining with Wright's stain.

Articular cartilage (20–40 mg) was dissected from the ends of both femurs of each animal and digested by incubation with papain. The concentration of sulphated proteoglycan in the digest was then determined by the 1,9 dimethylmethylene blue dye binding assay [3]. The proteoglycan content was expressed as μg glycosaminoglycan/mg wet weight cartilage and the IL-1-injected joint was compared with its contralateral control. In some experiments recombinant IL-1β (Genzyme) was injected. Also, the effect of 0.1 to 100 ng of lipopolysaccharide (LPS; Difco, E. Coli 0111 : B_4) was assessed.

Results

10 units IL-1 induced a high leukocyte infiltration at 4 h (Fig. 1) and these cells were > 90% polymorphonuclear leukocytes (PMN). At 24 h after injection the total leukocyte infiltration had subsided but there was significant mononuclear cell infiltration at this time (60–80% mononuclear cells). By 3 days after injection the leukocyte infiltration had disappeared. At no time was there a significant increase in joint diameter after IL-1 injection. Also, PGE_2 levels were not elevated in joint washes from the IL-1-injected joints and LTB_4 was not detectable in any joint wash.

There was no cartilage proteoglycan loss at 4 h after injection (Fig. 1). However, at 24 h, there was a significant reduction of $18.8 \pm 2.4\%$ (mean $\pm$ SEM, $n = 9$) in the proteoglycan content of the cartilage from the IL-1-injected joint compared to the contralateral control joint. 3 days after injection of IL-1, proteoglycan concentrations had returned to control values.

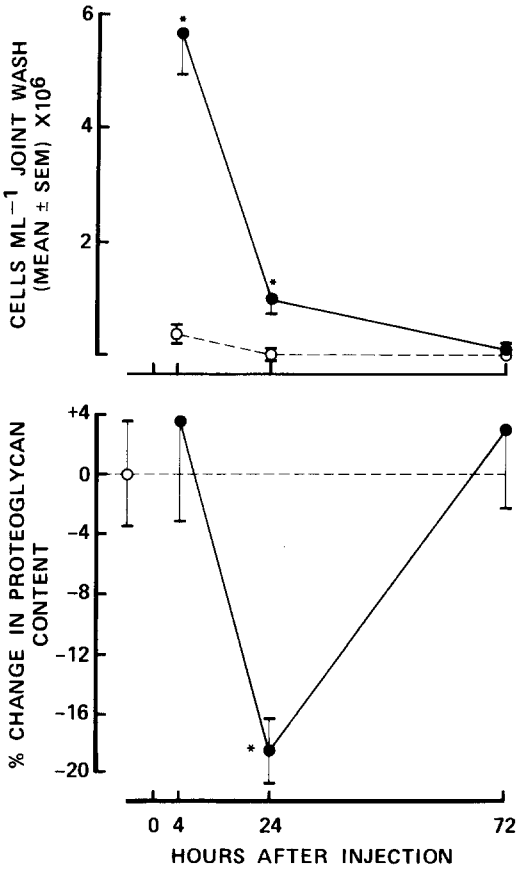

Figure 1
The top graph shows the effect of 10 units human highly purified IL-1 on leukocyte accumulation in rabbit knee joints 4–72 h after injection. IL-1 injected joint (●) contained significantly more leukocytes ($p < 0.01$) than control joints (○) at 4 h and 24 h but not at 72 h. The lower graph shows % reduction in proteoglycan content of cartilage from IL-1-injected joints (●) compared to control (○) at 4 h, 24 h or 72 h after injection. The cartilage from the IL-1-injected joint contained significantly less proteoglycan at 24 h ($p < 0.01$) but not at 4 h or 72 h. Data from ref. [4].

The leukocyte infiltration at 24 h after injection was dose-related, from $4.0 \pm 2.3 \times 10^5$ (mean ± SEM, n = 5) with 1 unit to $2.1 \pm 0.5 \times 10^6$ (mean ± SEM, n = 4) with 20 units. Mononuclear leukocytes were always predominant at this time.

Intra-articular injection of 10 units recombinant IL-1β produced a similar qualitative and quantitative response to the highly purified IL-1.

The *in vivo* chemotactic and cartilage degrading activities of these IL-1 preparations were abolished by pretreatment of the IL-1 preparation with 1% phenylglyoxal for 4 h at room temperature.

The IL-1 preparation was assayed for endotoxin by the Limulus test and was found to contain less than 0.1 ng/ml. Injection of doses of LPS up to 0.1 ng did not induce significant leukocyte infiltration at 24 h. However, LPS (1 ng to 100 ng) induced a dose-dependent infiltration of leukocytes at 24 h ($1.1 \pm 0.4 \times 10^6$, mean ± SEM, n = 6 to $3.3 \pm 0.6 \times 10^7$, mean ± SEM, n = 3) but this was not accompanied by any reduction in the proteoglycan content of the cartilage.

Discussion

This study shows that intra-articular injection of IL-1, at concentrations found in arthritic joints, induces PMN and mononuclear leukocyte infiltration into the joint space and causes cartilage degradation. Although IL-1 induces high PMN accumulation, this is not associated with joint swelling. Furthermore, the leukocyte infiltration and cartilage degradation were not associated with the production of LTB_4 or PGE_2. This indicates that these responses, which are characteristic of chronic erosive arthritis, are distinct from those induced by mediators of acute inflammation.

The studies with endotoxin show that leukocyte infiltration and cartilage degradation are not necessarily causally related and suggest that the degradative effect of IL-1 is not mediated via the inflammatory leukocytes. Rather, it is tempting to suggest that the cartilage degradation is mediated via the resident cells of the joint, the chondrocytes or the synoviocytes, and that the leukocyte infiltration occurs independently.

References

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