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Effect of Calcitonin on Different Inflammatory Models

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Abstract

The effect of synthetic salmon calcitonin was studied on adjuvant arthritis, pertussis vaccine edema, tuberculin skin reaction, passive direct Arthus reaction and nystatin edema. The results show that calcitonin inhibits these inflammatory processes.

The primary action of calcitonin is a direct inhibition of bone resorption by altering osteoclastic and osteocytic activity [1–4]. Moreover it enhances bone formation by an effect on osteoblasts [5]. Calcitonin has been reported to be beneficial in some skeletal diseases such as Paget's disease and osteoporosis [6, 7]. There is some evidence suggesting an anti-inflammatory activity of calcitonin: it has been shown that it inhibits acute inflammation such as dextrans and carrageenan edema [8, 9], and, alone or in combination with phenylbutazone or hydrocortisone, it consistently reduces the symptomatology of adjuvant arthritis [10, 11].

This paper reports our findings on the effect of calcitonin on various models of experimental inflammatory processes.

Materials and methods

Adjuvant arthritis was induced in Sprague–Dawley rats by an intradermal injection into the plantar surface of the right hind foot of 0.1 ml with a fine suspension of dead tubercle bacilli in liquid paraffin (concentration 5 mg/ml). The tubercle bacilli were derived from human strains PN, DT and C kindly supplied by Central Veterinary Laboratory, Weybridge, Surrey (U.K.).

The volume of the paws was measured with a volume differential meter [U. Basile, Comerio –Varese)] at the time of injection. Subsequent determinations were carried out daily in the first week and weekly in the remaining treatment period. Starting at day 0 synthetic salmon calcitonin (SCT was supplied by Armour Italia) in 16% gelatin vehicle was injected daily throughout the 8 weeks of the experiment. The dose employed was 10 MRC U/kg. Calcitonin was administered subcutaneously and the volume injected was 0.1 ml/100 g body weight. Controls received vehicle only.

Motility, severity of skin lesions and sensitivity to handling were evaluated. At the end of the treatment X-rays of paws and tails were taken.

Pertussis vaccine edema was induced in Lewis rats as described by ARRIGONI-MARTELLI et al. [12]. Calcitonin was administered subcutaneously daily from the sensitization to challenge (12 days) or from 3 days before to 1 day after the challenge.

Tuberculin skin reaction was induced in Lewis rats by injecting into the right hind paw 0.1 ml of 3 mg/ml suspension of *Mycobacterium tuberculosis* (H37 Ra strain) in mineral oil. Twelve days later the animals were skin tested by injecting intradermally 0.1 ml of saline containing 10 μg of PPD. The skin reaction was evaluated (wheal diameter) 24 and 72 h later. Dosing regimes were as described for the pertussis vaccine edema.

Passive direct Arthus reaction was induced in Sprague–Dawley rats as described by MEGEL et al. [13].

Nystatin edema was induced as described by ARRIGONI-MARTELLI et al. [14].

Results

Figure 1 shows the changes in volume of the uninjected paws of arthritic rats after treatment with 10 MRC U/kg of calcitonin and without treatment. A marked inhibition of paw edema was obtained especially at the initial and final phases of treatment. The inhibition was significant at the second week ($P < 0.05$) and from the fifth week to the end of the experiment ($P < 0.01$).

X-rays show in control animals considerable alterations of bone structure of paws and tail with a reduced bone density. In treated animals less diffuse structural alterations of bones and an improvement in bone density were noted (Figs. 2, 3). In addition a better motility, a lower number

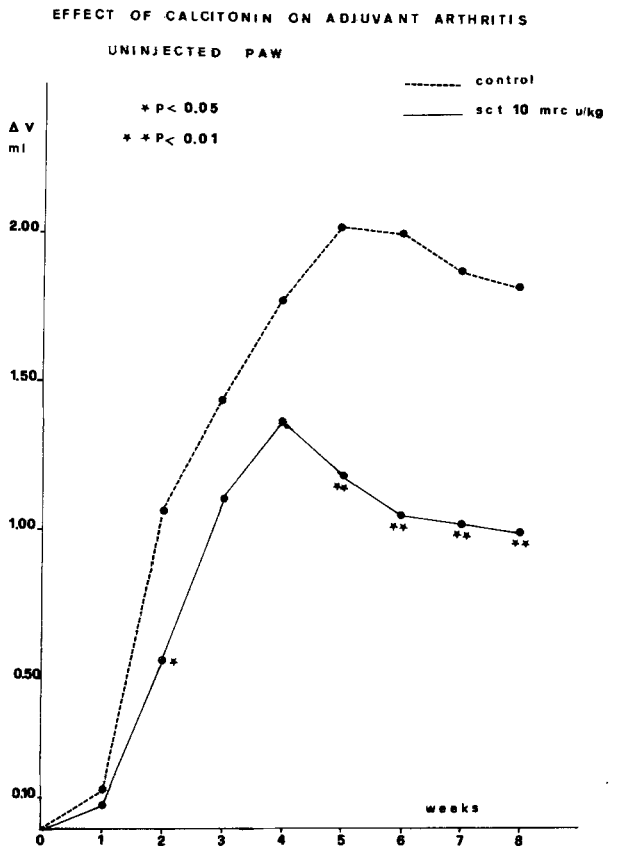

Figure 1

of affected joints and a minor sensitivity to pain were noticed.

20 U/kg administered daily subcutaneously from the sensitization to challenge significantly inhibited only early phase of the pertussis vaccine reaction (6–48 h after the challenge). The more advanced phase remained unmodified. The administration of calcitonin around the challenge similarly resulted in a significant inhibition of the early phase of the reaction, whereas the more advanced phase was enhanced (Fig. 4).

The skin reaction to tuberculin was clearly inhibited in rats dosed with calcitonin (20 U/kg s.c. daily) from the sensitization to challenge. When calcitonin was administered around the challenge a significant reduction of the wheal diameters was observed 24 h after challenge. However, 72 h later the intensity of the skin reaction was increased (Table 1).

The effects of acute treatment with calcitonin at various times before the challenge on passive direct Arthus reaction are reported in Table 2. It is apparent that calcitonin substantially inhibits this reaction only when administered shortly before the subplantar injection of bovine serum albumin.

The development of nystatin edema was inhibited in rats administered subcutaneously with calcitonin 1 h prior to nystatin injection. The delayed phase of the edema was however unaffected. The administration of calcitonin to animals with inflammation already developed was ineffective (Fig. 5).

Discussion

These results show that repeated calcitonin administration causes a delay in the appearance of certain immunologically mediated inflammatory processes such as pertussis vaccine edema and tuberculin skin reaction. Single administration inhibits the early phase of nystatin edema and the passive direct Arthus reaction, probably the simplest of the complex-induced lesion disease [15]. One may only speculate on the mechanism of this action of calcitonin. However, it may be suggested that the decrease of total and ultra-

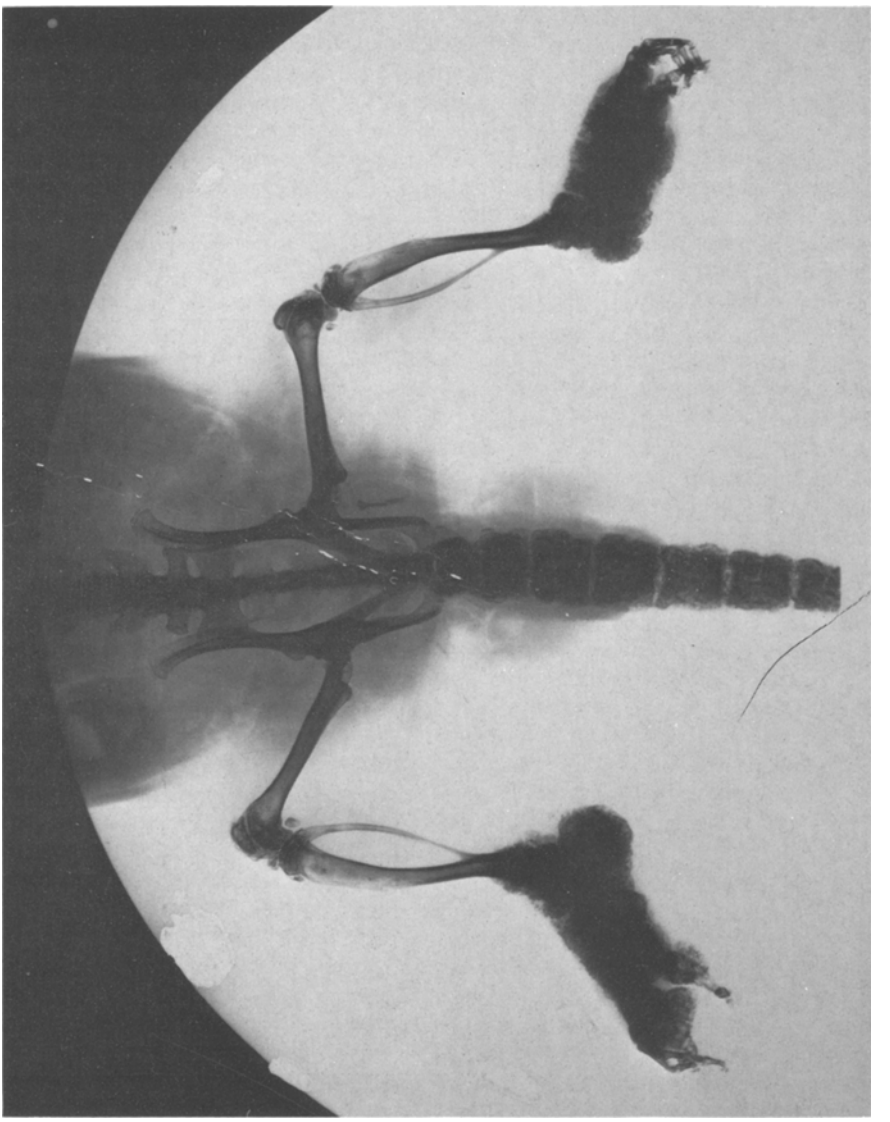

Figure 2
Radiograph of hind limbs and tail of an arthritic rat 8 weeks after the injection of tubercle bacilli into the hind paw.

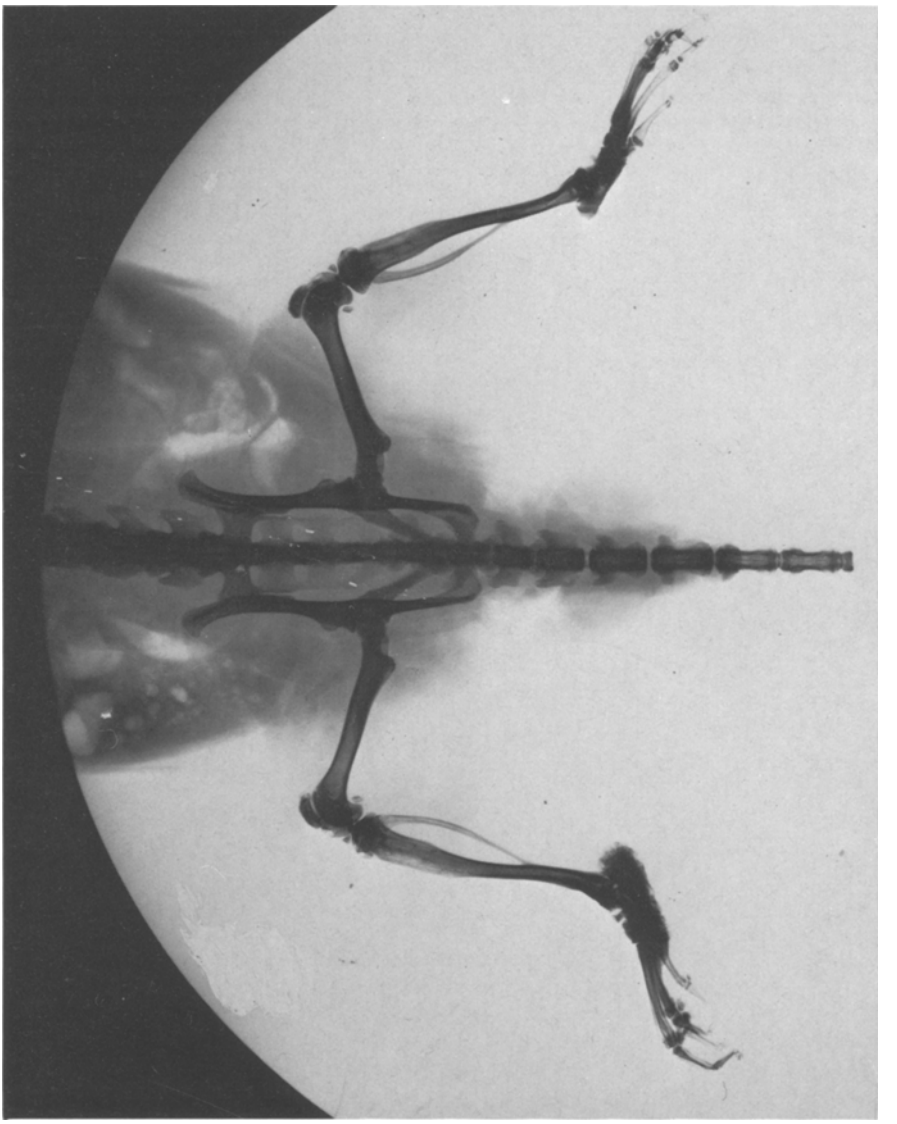

Figure 3
Radiograph of hind limbs and tail of an arthritic rat treated with SCT (10 MRC U/kg) 8 weeks after the injection of tubercle bacilli into the hind paw.

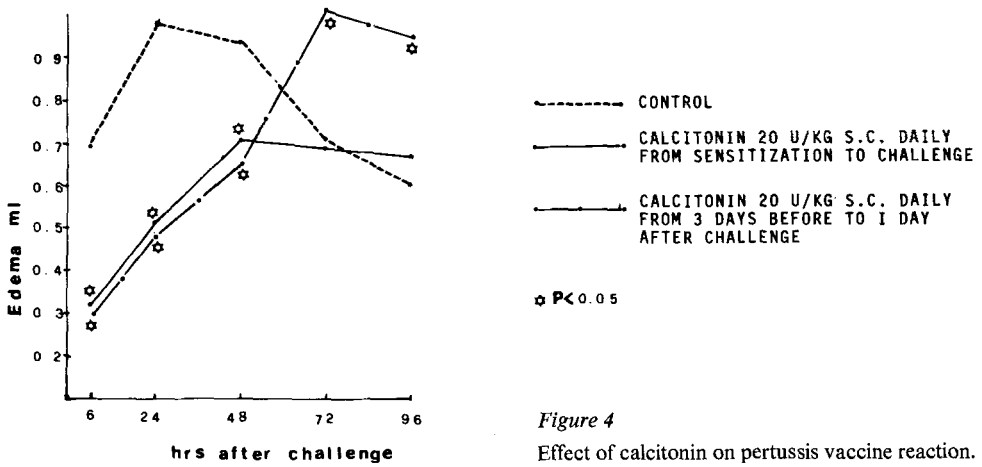

Figure 4
Effect of calcitonin on pertussis vaccine reaction.

Table 1
Effect of calcitonin on tuberculin skin reaction.

Treatment	Wheal diameters mm ± S.E.		*n*
	24 h	72 h	
Control	11.2 ± 3.6	9.5 ± 3.4	10
Calcitonin 20 U/kg s.c. daily			
(a) from sensitization to challenge	3.9 ± 2.1	3.4 ± 2.7	5
(b) from 3 days before challenge to 1 day after	5.3 ± 2.4	14.2 ± 2.1	5

Table 2
Effect of calcitonin on passive direct Arthus reaction.

Treatment	Edema ml ± S.E.	*n*
Control	0.87 ± 0.12	8
Calcitonin 20 U/kg s.c.		
1 h before challenge	0.41 ± 0.11	5
3 h before challenge	0.47 ± 0.13	5
24 h before challenge	0.75 ± 0.12	5

filtrable calcemia occurring after calcitonin administration may lead to a suppression of prostaglandin synthesis [9], and plays a role in the reduction of soft tissue inflammation. A contri-

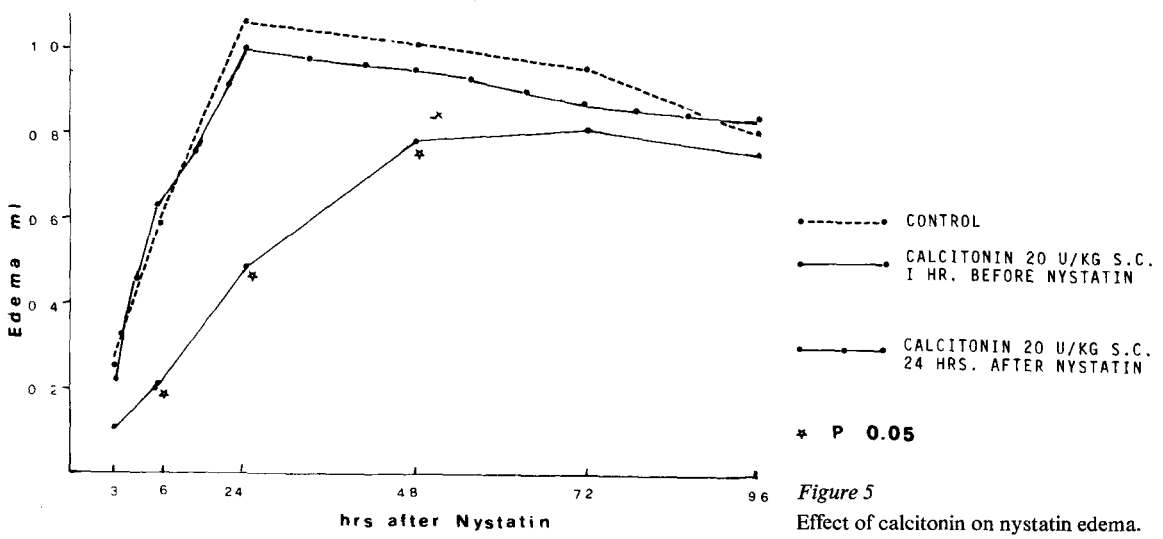

Figure 5
Effect of calcitonin on nystatin edema.

butory factor may also be the ability of calcitonin to produce electrolyte shifts [16]. The beneficial action of calcitonin on adjuvant arthritis is, however, not limited to an inhibitory effect on soft tissue edema, it also includes decreased severity of bone alterations, thus suggesting either an inhibition of bone resorption and an inhibition of bone formation. The finding that calcitonin administered around the challenge is able to inhibit the early phase of an immunologically mediated inflammation and to enhance the late phase suggests the possibility that the compound may interfere with immunological mechanisms. A modification of Ca^{++} levels could in fact account for an alteration in the immune mechanism [17].

Acknowledgments

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