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Effect of Calcitonin on Carrageenan Foot Oedema

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Abstract

The effect of salmon calcitonin (SCT) on acute inflammation was tested in carrageenan induced foot oedema of the rat. A considerable inhibition of the oedema was obtained with 20 MRC U/kg of SCT. The injection of SCT is followed by decrease of calcemia. A hypothesis of possible inhibition of prostaglandin (PG) synthesis and/or release, caused by decrease of calcemia, is advanced.

Introduction

Pharmacological actions of calcitonin have recently been extensively studied. The primary action of this hormone is on bone, where it depresses the function of cells that promote bone resorption [1–3]. It is apparently an agent of great promise for the treatment of some skeletal diseases e.g. Paget's disease [4–8], osteoporosis [9, 10] and bone tumours (unpublished data).

However, relatively little is known about the effects of this hormone on inflammatory processes. Porcine and human calcitonins have been reported to produce inhibition of increased vascular permeability caused by dextran in the rat hind paw [11]. Attempts to show possible clinical use of calcitonin in preventing bone lesions secondary to inflammatory states were made by BOBALIK et al. [12]: the results obtained by these authors show clearly the inhibition by salmon calcitonin of rat adjuvant arthritis.

Also the disappearance of oedema, cyanosis, perspiration and pain during the therapy of Sudek's disease and rheumatoid arthritis with porcine calcitonin was noticed [13].

These last remarks suggested us to investigate the effect of calcitonin on acute inflammation. Carrageenan induced oedema in the rat foot is widely used as a model of inflammation in search for new anti-inflammatory agents. The use of this model of inflammation is mainly based on the observation that the ability of drugs to suppress the oedema correlates with their therapeutic activity in chronic inflammation in man.

Materials and methods

Male Sprague-Dawley rats (150–200 g) were used.

Carrageenan (Viscarin Rex 7191) and synthetic salmon calcitonin were respectively supplied by Marine Colloids Inc. (Rockland, Maine, USA) and Armour Italia S.p.A. (Verona).

Carrageenan foot oedema was produced by injection into the plantar surface of the hind paw of 0.1 ml of a 1% carrageenan in sterile saline.

The volume of the paw was determined at the time of injection with a volume differential meter (U. Basile, Comerio [Varese]). Subsequent readings were carried out hourly for 6 hours and after 24 hours and compared with the initial reading. SCT in 16% gelatin vehicle was injected i.m. in a volume of 0.1 ml/100 g body weight, 1, 2 and 4 hours before carrageenan. The doses employed were 10, 20 and 50 MRC U/kg.

Assays of total and ultrafiltrable serum calcium were made after injection of 20 MRC U/kg [14].

Results and discussion

A single injection of 20 MRC U/kg of SCT, made 1, 2 or 4 hours before carrageenan, inhibited to the same degree the development of oedema. Figure 1 shows the increase of foot volume in treated and control animals. The suppression of the oedema was statistically significant at 4 hours ($p < 0.01$) and at 5 and 6 hours ($p < 0.05$): the inhibition was respectively 35, 30 and 26%. The injection of 10 MRC U/kg reduced the oedema by 15% at 4 hours. The inhibition produced by 50 MRC U/kg was not significantly different from that obtained with 20 MRC U/kg.

Di Rosa and Willoughby [15] reported that carrageenan oedema is mediated by a release of histamine, serotonin, kinins and prostaglandins. The PGs seem to be mediators of the last phase ($2^1/_2$–6 hours).

The drug did not influence the early development of the oedema (histamine, serotonin and kinin phases), even when SCT was administered 4 hours before carrageenan. There was a significant inhibition only during the prostaglandin phase.

Decrease of total and ultrafiltrable calcemia occurs after injection of SCT: such decrease is significant ($p < 0.05$) from 1 to 10 hours. After 12 hours the calcium level slightly rises and after 24 hours returns to the normal values (Fig. 2).

The mechanism underlying the inhibition of the oedema may possibly be based upon a partial suppression of the prostaglandin phase due to the decrease of calcemia which could inhibit the synthesis and/or the release of PGs, thus affecting the aspects of the inflammatory response mediated by PGs (i.e. vascular permeability, chemotaxis for leucocytes, transition from acute to chronic inflammation, etc. [16]). This hypothesis is supported by the inability of SCT to block the oedema produced by injection of 100 mg of PGE_1 in the rat paw.

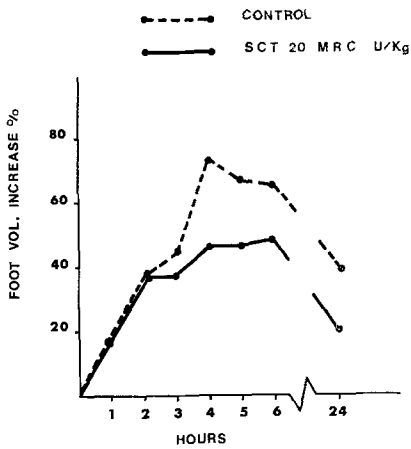

Figure 1
Rat hind paw response to the injection of carrageenan. SCT was injected i.m. 1 hour before carrageenan. Abscissa shows time in hours after carrageenan injection; ordinate shows percent increase of foot volume compared to controls. Each point represents the mean of 3 experiments from 8 rats.

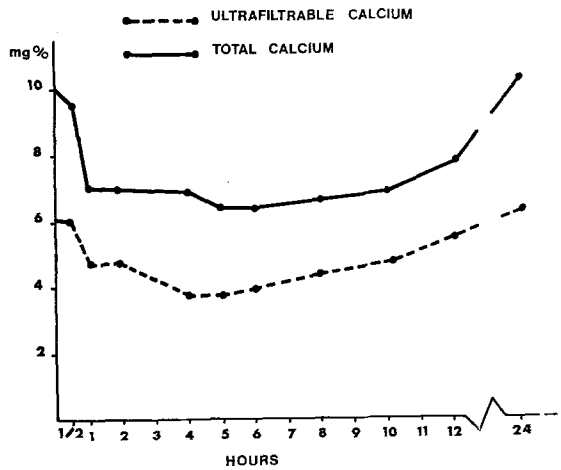

Figure 2
Blood calcium levels (mg/100 ml) after injection of 20 MRC U/kg SCT. Each point represents the mean of 6 rats.

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