Calcitonin-Induced Analgesia: An Unusual Hormone Specificity

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Upon direct injection into the central nervous system of laboratory mammals, salmon calcitonin (sCT) is known to produce a variety of effects: antinociception (1), anorexia (2), and achlorhydria (3). Comparative studies (4, 5) on the anorectic potency of calcitonins of various animal origins have provided the results supporting the classical concept established for the hypocalcemic activity that the hormone of fish origin is biologically far more potent than the mammalian congeners (6).

However, it was recently noticed that in the dose which did develop complete anorexia in rats, sCT failed to induce antinociception, while porcine calcitonin (pCT) even in the same molar dose appeared to elicit antinociception (7). This is an unexpected observation from the above concept.

Wistar male rats weighing 250–350 g were used. sCT (4500 U/mg) was the synthetic product and pCT (170 U/mg) the natural one from the Armour Pharmaceutical Co. (Kankakee, IL, U.S.A.). Intracerebroventricular cannulation was done as described previously (4). The antinociceptive activity was evaluated by the method of Randall and Selitto (8). Baker's yeast (20 w/v % in saline, 0.10 ml/rat) was injected into either one of the hindlimbs. Two hr later, peptide in vehicle (0.1 M ammonium acetate buffer, pH 4.7) or vehicle alone was administered intracerebroventricularly or subcutaneously.

The serum Ca level was estimated by the method of Gitelman (9).

As shown in Fig. 1, the anorectic dose of sCT (0.062 nmol/rat), which usually resulted in complete anorexia lasting about 24 hr, was unable to increase the response threshold. This dose of sCT is known to cause long-lasting hypocalcemia, possibly by leaking into the systemic circulation and acting peripherally (10). In the doses tested, pCT did not induce either anorexia or hypocalcemia, but elevated the response threshold to

Fig. 1. Antinociception inducible by intracerebroventricular injection of calcitonins. At time 0, vehicle (10 μ l/rat, ○—○), sCT (0.062 nmol/rat, ●—●) and pCT (0.062 nmol/rat, ▲—▲) were injected. Each point and bar represents the mean $\pm$ S.E. (5–6 rats/mean), and the asterisk indicates a significant increase of the threshold (*: $P < 0.05$ and **: $P < 0.01$).

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Fig. 2. Antinociception inducible by subcutaneous injection of calcitonins. At time 0, vehicle (1.0 ml/kg, ○—○), sCT (1.6 nmol/kg, ●—●), and pCT (0.16 nmol/kg, ▲—▲ and 1.6 nmol/kg, ▼—▼) were injected. Each point and bar represents the mean $\pm$ S.E. (6–7 rats/mean), and the asterisk indicates a significant increase of the threshold (*: $P < 0.05$ and **: $P < 0.01$).

a small but significant extent.

Even when injected systemically, pCT was found to be active. Subcutaneous injection of 1.6 nmol/kg produced significant antinociception with a rapid onset and at least 30 min duration (Fig. 2). In contrast, sCT (1.6 nmol/kg) was again inactive in such a high dose level that decreased the serum Ca^{2+} level from 9.7 mg/dl to 8.6 at 1 hr after injection.

The antinociceptive effect of pCT developed only on the limb into which yeast was injected. pCT has so far failed to increase the response threshold of the untreated hindlimb.

Though more detailed studies using other assay methods of antinociception are to be done, the results reported herein suggest that pCT even after central injection may exert its antinociceptive effect by acting on the peripheral site, and it is possible that the underlying mechanism is quite different from the ones conceptualized for the other actions of calcitonins (11, 12).

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