Calcitonin-Physiological, Pharamacological and Clinical Role in Bone Diseases

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Abstract : Since its discovery in 1961, calcitonin has been identified as an endogenous hormone of several animal species including human. It has also been found to have potent therapeutic properties, leading to the extraction or synthesis of various types for this purpose. Many of the findings regarding both its physiological and pharmacological properties remain discrepant, but it is probably safe to describe calcitonin as a hormone which, in combination with many other factors, has a corrective and /or regulatory effect on phosphorus and calcium metabolism - for example in the maintenance of calcium balance and skeletal mass. It does this by controlling bone remodelling and the uptake, storage and elimination of calcium. It is also active in situations involving high calcium demand such as occur during bone growth, pregnancy and lactation, and after eating.In addition. it is involved in certain CNS mechanisms of pain control and neuro-modulation. In therapeutic use, calcitonin has demonstrated a low level of toxicity, with relatively minor side-effects and a wide safety margin. Its efficacy in diseases characterized by bone loss or disorders of bone remodelling is well established, and it will probably prove useful in other diseases involving bone.

INTRODUCTION

Calcitonin is an endogenous regulator of calcium homeostasis, acting principally on bone. Its effect, which was first noted by Copp in 1961[1,2] is to lower the blood level of calcium due-as was found some years later-to a direct inhibitory action on osteoclast activity. In man it is secreted by the thyroid and not,as was originally thought[3] by the parathyroids.The normal human thyroid contains 1-100 ug calcitonin, while the amount secreted per day has been reported to be 50-250 ug by one group of workers[4] and 13.8 ug by another[5].

Calcitonin have also been isolated from other species (ox, chicken, salmon, eel, etc.) and five types have been synthesized. Many synthetic analogues have also been prepared, but so far only four calcitonins are in general medical use-synthetic salmon and synthetic human calcitonin, natural porcine calcitonin and a synthetic derivative of eel calcitonin (aminosuberic 1,7-eel calcitonin).

The principal indications for the therapeutic use of calcitonin are disorders involving hypercalcaemia, Paget's disease of bone, osteoporosis, vitamin-D intoxication, bone metastases, and chronic pain associated with bone disease. However, studies of the physiological and pharmacological effects of calcitonin, many of which are not yet fully understood are leading to new and unexpected therapeutic uses. Calcitonin has for instance, already found clinical application in the treatment of acute pancreatitis.

Chemically the calcitonin are peptide hormones with molecular weights around 3500. The molecule of a chain of 32 amino acid residues with a proline amide group at the C terminal. A disulphide bridge between the cysteine in positions 1 and 7 forms a ring of 7 aminoacid residues at the N terminal, which carries a free amino group (Fig. 1). The amino acid composition ofthe central part of the chain varies from one

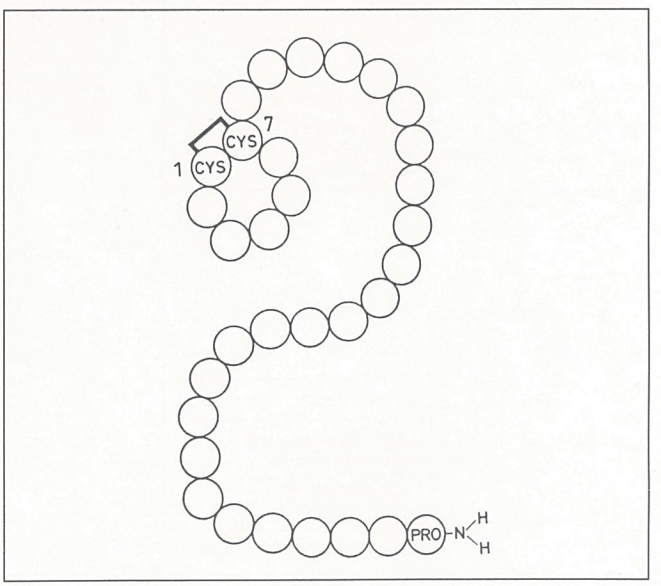

Fig. 1 Basic features of the calcitonin molecule

calcitonin to another, similarity or dispartity of structure being in no way correlated with activity.

Reported blood levels in healthy subjects vary widely, which probable reflects the variable specificity of the antibodies used in radioimmunoassays and the difficulty of the techniques themselves. Quoted levels range from 1 to 500 pg/ml plasma[6,10]; 75 percent of healthy subjects have blood levels below 100 pg/ml[8] the mean level being between 30 and 90 pg/ml[11,12]. Blood levels are an excellent biochemical marker for diagnosing certain diseases and for monitoring the effects of treatment.However, in view of the wide normal range, blood levels should always be determined with the same assay technique and, if possible, with antiserum of the same specificity.

PHYSIOLOGICAL FUNCTIONS

Although its actions are not yet fully understood, endogenous calcitonin seems to exert effects at many sites, and receptors are present in many tissues, including bone[13-15] and kidney cells[13,14,16,17] the central nervous system[18-21] ,and pituitary gland[19,22] testicular Leydig cells[23] ,lymph cells[24,25] and some types of tumour[26-29] (Fig. 2).

The principle physiological role of endogenous calcitonin is almost certainly the regulation of calcium metabilism, chiefly by helping the body to deal with episodes of "calcium stress", i.e. preventing calcium excess. As one of the major constituents of the body's internal milieu, calcium plays a vital part in the maintenance of both structural (skeletal and muscular) and other (endocrine,nervous and circulatory) systems. It is involved for example in the control of cellular permeability, neuromuscular excitability, muscular contraction, the activation of certain enzymes (lipase, succinyl dehydrogenase, trypsinogen ATPase) in endocrine secretion in cardiac function and in blood coagulation[30]. Calcium also directly or indirectly controls the movement of other mineral ions, such as phosphate and magnesium as part of the process of maintaining ionic equilibrium. At times of calcium stress-e.g. during growth, pregnancy, lactaion and after eating-calcitonin protects the skeleton by inhibiting osteoclast activity and proliferation,

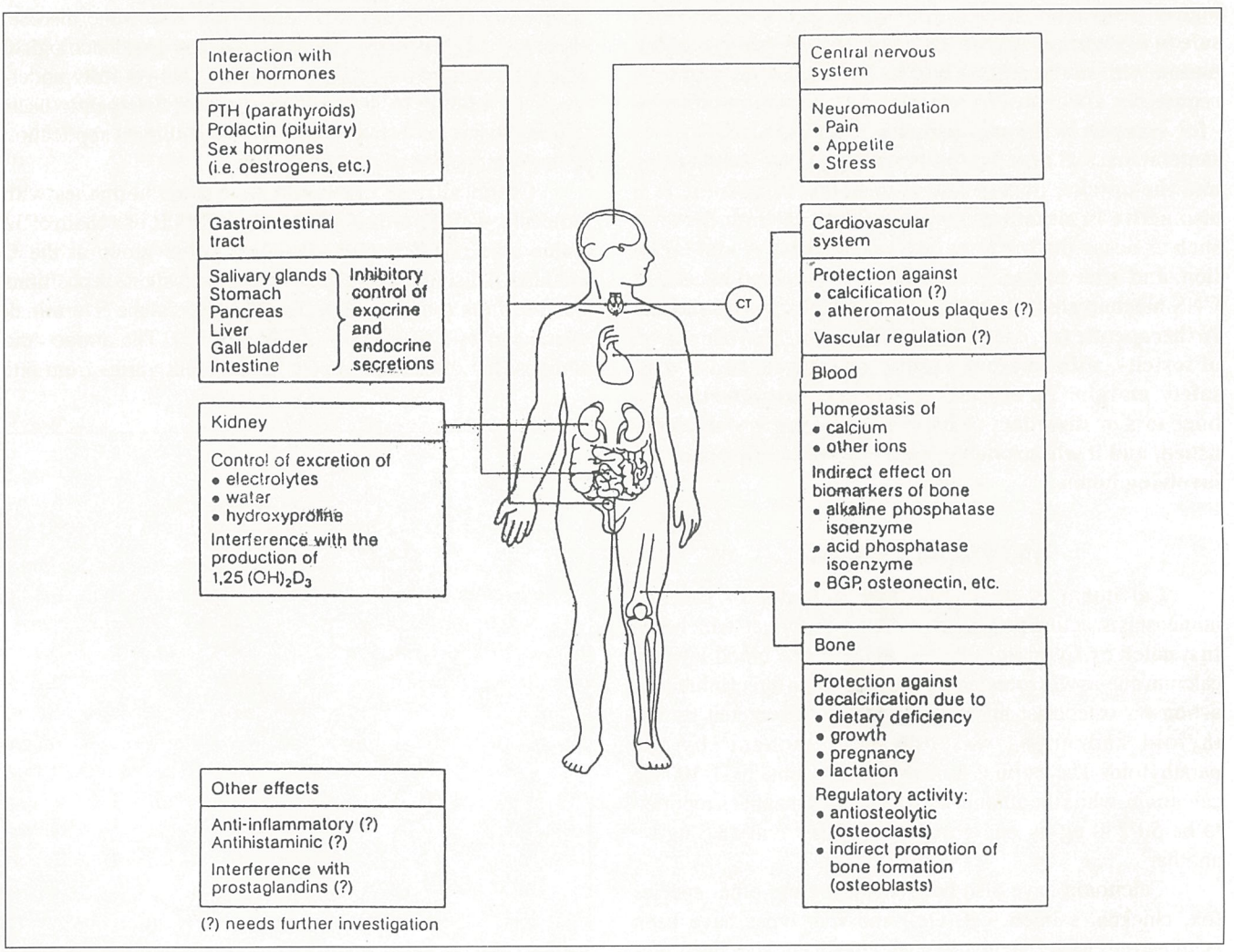

Fig. 2 Diagram showing the main physiological of endogenous calcitonin

thereby reducing bone resorption and remodelling[31]. It is thought to control osteoclast activity by regulating the movement of calcium between the extracellular, intracellular and mitochondrial compartments, in interaction with PTH. Inside the cell calcium may remain in the free sate in the cytosol or be reversibly deposited in the mitochondria[32-34] and calcitonin is belived to promote this deposition, an effect that is enhanced by phosphates, which increase the ability of mitochondria to accumulate calcium[35,36]. PTH, on the other hand indirectly promotes calcium efflux from the mitochondria into the cytosol and thence in the direction of the extracellular fluid[37-39]. This redistribution of calcium during osteolysis is a accompanied by increased release from bone and increased reabsorption from the renal tubules. The net gain or loss in total cell calcium depends on the concentration ratio of intracellular to extracellular calcium[37-41]. Some authors suggest that the primary effect of calcitonin on bone mineralization is to regulate the uptake of phosphate by bone cells, the combination of phosphate and calcium leading to precipitation of hydrozyapatite. According to this hypothesis the effect of calcitonin on blood calcium is simply a consequence of mineral nucleation after phosphate uptake[34,42] and is either distinct from its effect on bone resorption or else linked via the inhibitory action of phosphate on resorption[43].

PHARMACOLOGY

The wide-ranging effects of pharmacological doses of calcitonin suggest that the hormone has therapeutic potential beyond its primary role in calcium regulation. Its action on bone consists primarily inhibition of resorption, which it achieves by reducing the activity and number of osteoclasts[44].

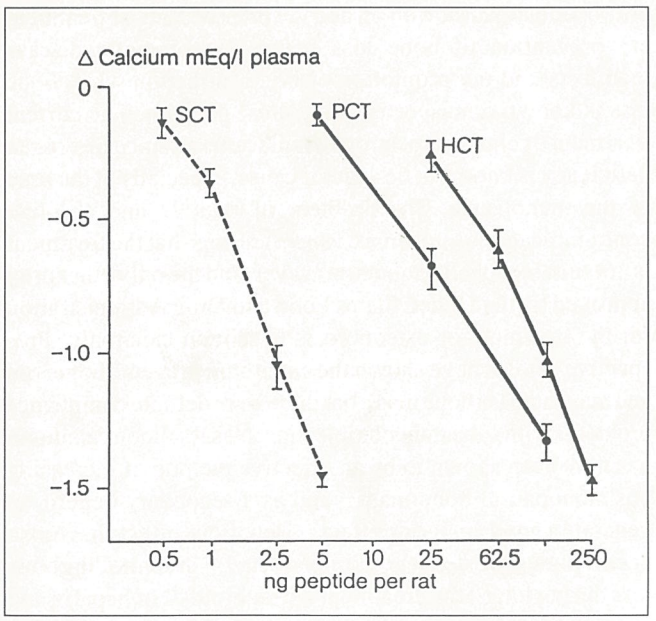

Fig. 3 Dose/hypocalcaemic response curves for human (HCT), pig (PCT) and salmon (SCT)

This anti-osteolytic effect is thought to retard bone demineralization and breakdown of the matrix. By depressing osteoclast activity, calcitonin may also indirectly osteoblast activity, which might explain its apparent success in Paget's disease in normalizing bone turnover. However, it has also been suggested that it might promote bone formation through stimulation of osteoblasts, chondrogenesis and matrix mineralization[45] and it is also possible that it indirectly prolongs the formation phase of the bone remodelling unit's cycle. however, these hypotheses are still controversial and need further investigation. These effects are reflected in reduced blood levels of calcium and phosphate. The magnitude of the hypocalcaemic effect (Fig. 3) depends on the dose[46,47] the concentrations of other present (especially phosphate), and interactions with other hormones, particularly PTH. The effect also depends on the level of blood remodelling activity[48]. In healthy adults the hypocalcaemic response to a normal dose is slight, blood calcium levels falling by only 3 to 5 mg/l at 1-4 hours after administrations. However, when bone remodelling activity is high, as in children and patients with certain bone diseases, blood calcium may fall by as much as 15 mg/l. The principle effect of calcitonin on the central nervous system is analgesia[49] and it has been reported to relieve bone due to tumour metastases[50,51], Paget's disease[52] and osteoporosis[53]. How this effect is mediated is uncertain. Suggested mechanisms include an effect on calcium flux in the neuronal membrane[49] an action at specific central receptors[54] an increase in B-endorphin levels[53-56], inhibition of prostaglandin synthesis[57] or simply an indirect result of general improvement in painful bone lesions resulting in reduced pain perception at central level. The activation of adenylate cyclase in bone and kidney cells by PTH is not blocked by calcitonin and the parathyroid gland continues to function normally during long-term treatment with calcitonin[58,59] and calcium. Hyperparathyroidism is not a typical feature of medullary carcinoma of the thyroid[60] the two hormones acting at different receptors in bone and kidney[44,61,62].

CALCITONIN IN THERAPEUTIC USE

The principle calcitonin in therapeutic use are synthetic salmon calcitonin (SCT), synthetic human calcitonin (HCT), natural porcine calcitonin (PCT) and the 1,7 aminosuberic derivative of eel calcitonin (ECT). SCT and ECT are 20-40 times more potent than HCT and PCT (Table 1). This is thought to be due to their greater intrinsic biological activity at their specific receptors to their greater resistance to enzyme degradation[30] and-at least in the case of SCT - to a 2-3 times slower metabolic clearance rate. No correlation has yet been found between blood levels and clinical efficacy, however, and although the peak concentration is reached within an hour of administration, the maximum hypocalaemic effect occurs later and sometimes persists after the blood level has fallen below the threshold of detection (depending on the assay method used) (Fig. 4). The introduction of synthetic forms of

Table 1: Hypocalcaemic activity of the calcitonins

Species	Activity (IU/mg)	Activity (mg/unit)
Salmon I Salmon II Chicken Asu[1,7]-eel	4000-6000	0.00017-0.00025
Salmon III Eel	2000-4000	0.00025-0.0005
Rat Ox	-400	-0.0025
Sheep Pig Man	100-200	0.005-0.01

calcitonin has facilitated its therapeutic use. Established indications include hypercalcaemic states with or without bone involvement, such as bony metastases and vitamin D intoxication[63,64], Paget's disease of bone[65] ,osteoporosis[66-69], chronic pain associated with bone disease[70], reflex sympathetic dystrophy(sudeck's disease), and acute pancreatitis as an adjunct to primary therapy[71]. Hypercalcaemia and hypercalcaemic crisis due to excessive osteolysis associated with cancer of the breast, lung or other organ, myeloma, hyperparathyroidism, immobilization, or vitamin D intoxication respond well to calcitonin in both short-term and long-term use. Paget's disease (osteitis deformans) responds well, especially where there is bone pain with neurological complications, high bone turnover (as shown by raised serum alkaline phosphatase and urinary hydroxyproline levels) or progressive bone lesions with partial or repeated fractures. Osteoporosis is such a large

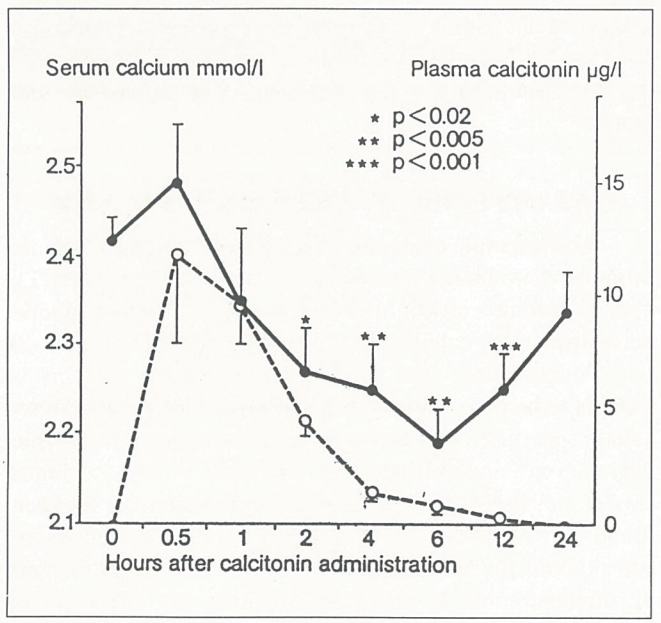

Fig. 4 Serum calcium (-) and plasma calcitonin (fi) levels (mean+ SEM) in 7 Gagetic patients after a single dose of synthetic HCT 100 IU s.c.

Table 2 : Adverse reactions occurring with calcitonins, especially after i.m. administration

Gastrointestinal symptoms	Nausea Vomiting Abdominal pain Diarrhoea Unpleasant metallic taste in the mouth
Vascular symtoms	Facial flushing Sensation of facial warmth Sensation of warmth affecting the hands Tingling in the extremities
Local symtoms	Erythemn at the site of injection. Pain at the site of injection
Renal symtoms	Increased frequency of micturition. Polyuria
Allergic symtoms	Rash

problem both to individual sufferers and to their respective societies and health care systems that it merits separate discussion. It is estimated that in Europe, the USA and Japan there are 75 million cases of osteoporosis (with femoral neck and / or vertebral crush fracture). More than 40 percent of women over seventy years of age sustain a fracture and 15-20 percent of women sustaining a fracture of the femoral neck die within 12 months. The direct and indirect costs of osteoporosis thus run to billions of dollars and any successful intervention will cleary have a major public health benefit, especially as life expectancy is increasing. The majority of osteoporosis patients are postmenopausal women and the present aims of treatment are prevention of bone loss before symptomatic disease manifests and the promotion of bone formation when bone loss is known or suspected on clinical grounds. The current treatment of choice is oestrogen replacement, since oestrogen deficiency is known to be a major cause, especially at the time of the menopause. The problem of relative and absolute contraindications (e.g. breast cancer) means that the treatment is not suitable for all patients, however, and the only other drug approved by the United States Food and Drug Administration for the treatment of osteoporosis is salmon calcitonin. Prospective studies have shown the calcitonin prevents bone loss and may increase bone mass, but there were definite compliance problems with subcutaneous injection. Nasal salmon calcitonin has now been shown to be an effective method of increasing postmenopausal bone mass[72] and as a secondary benefit, to generate a good analgesic effect[73]. Beneficial effects have also been reported in osteogenesis imperfecta[74,75] in controlling bone loss during long-term treatment with steroids[76] or heparin and in chronic renal insufficiency associated with excessive

osteoclast activity[77]. In Paget's disease SCT and HCT have comparable effects at equipotent hypocalcaemic doses and their efficacy is normally maintained for 3-20 months. In hypercalcaemia, SCT and ECT are the calcitonins of choice. The principle side effects of calcitonin are shown in Table 2. Subcutaneous administration is tolerated better than intramuscular or intravenous, while intranasal administration is better than either, giving rise to very few unwanted effects. In fact, the advent of the intranasal form is an exciting development because it has made an effective but "problematic" drug fully acceptable to patients, overcoming the problem of compliance and thereby helping it to realizes its full therapeutic potential.

ACKNOWLEDGEMENTS

The author wishes to acknowledge the considerable help of Stephen Cooper BA and Carole Ritchie, MA in the preparation of this article.

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