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Calcitonin: Survey of new anatomy data to pathology and therapeutic aspects

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ABSTRACT

Since the discovery of calcitonin (CT) reports have questioned the physiological role of human CT in regulating calcemia. This peptide is produced out of the CT/CGRP gene splicing along with other factors or hormones, including somatostatin by synonymously called parafollicular cells, C thyrocytes or C cells located in the thyroid glands. The C cells have recently been proven to originate out of the ultimobranchial anlage of the pharyngeal endoderm instead of the neural crest cells as indicated in all textbooks. Both blood and urine CT and procalcitonin (proCT) found in human and other mammals can also be secreted by cells located outside the thyroid glands. Taking account of dietetic calcium intake, CT assists in the homeostasis of bone mineral mass during growth, lactation, and pregnancy, hypo- and hyper gravity along with other paracrine thyroid secretions. Excess CT level in tissue fluids, needle aspirations and, now proCT, can diagnose sepsis, medullary thyroid or other carcinomas; caution to be taken with ectopic CT and gender-difference levels. Salmon CT as diurnal oral delivery seems, if proven not toxic, best suited to continue preventing or treating several defects, especially osteoporosis, orthopedic-related pains, perinatal or acute, fatal hypercalcemia. Contemplating old with recent physiological clinical results, human longitudinal morphologic and molecular data dealing with C cells and their paracrine interactions are few while only animal studies make us know much about CT. Human samples out of biopsies or cadavers should be further endeavored from development to aging to fully correlate normal with extreme or peculiar pathologies.
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Contents

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1. Introduction

'*Plus est en vous*' [There is more in you]

House Van Gruuthuse, Brugge.

Like many other hormones, pathologic observations and experiments that lead to the discovery of the calcitonin (CT) were performed under pathologic rather than normal physiological conditions out of small mammals (e.g. dogs, rats, pig, guinea pig). Initial observations were made by removal of the thyroid and parathyroid glands of dogs in Sanderson's laboratory [1,2]. Later, further observations about CT involved the delivery of a very high dose of calcium to dogs, rats and sheep that resulted in a significant fall in blood calcium and regulated phosphate uptake observed after parathyroidectomy [1–15]. These data led these authors to claim the existence of a new hormone whose crucial role is to control the body fluids' level or 'tone' of calcium, i.e. calcemia. Originally, and wrongly though, this hormone has been thought to be released by the parathyroid glands, so the large number of publications dealing with parathyroid [e.g. Refs. [1–13]]. It was only a year later after the original observations [3] that the same group followed by others demonstrated that the C cells in rat and dog thyroid glands were the true source of CT [13]. This 32-amino acid protein hormone was isolated and purified out and proven to originate from those C cells of the thyroid gland. Hence the name 'thyrocalcitonin' or 'calcitonin' to indicate its origin and function of the hormone [16–20]. Both terms are accepted by the World Health Organization and used in pharmaceutics.

Sources of CT have also been extracted from ultimobranchial bodies of domestic fowl and fishes and this CT have been formulated to be used as medication [21–23]. Salmon CT (sCT) has been found to be most physiologically active CT to treat hypercalcemia [21,22] and osteoporosis [23].

This survey was initiated after previous observations describing crinophagy in the thyroid glands in both C and T thyrocytes of genetically obese rats [24] where one became intrigued about CT functions since this rat strain survived with high, toxic calcemia [22,23,25,26].

Based on earliest data, this report adds not only the newest information about the embryological origin of the C cells with the intent to comfort and stimulate further morphologic biomedical studies and their interrelationships with the adjacent thyroid gland cells and tissues to encourage further studies to clarify some paracrine functions and pathology already known through comparative physiology or histopathology.

Even though CT was the topic of several reviews [e.g. Ref. [27]], especially, another more recent one [28], it was found necessary to add this survey to encompass not only those very recent crucial developmental findings in regards with normal development but also to convey the difficulties to obtain precious old data out of human tissues buried in archival state. Data from C cells from fetal to aging are needed to comfort the physiologic status of C cells, found to be interacting with the T thyrocytes because CT can regulate calcemia and is a marker for other pathologic etiologies of neo- or perinatal status and other diseases, including sepsis, bone repairs, ageing, and cancers. Finally, the usage of synthetic CT (sCT) is also evoked because this medication needed to acutely reduce a high and toxic serum calcium level, to treat osteoporosis as well as pain associated with bone surgeries may have a carcinogenetic activity. However, this warning based on statistics [29] appears in another study to suggest no such toxicity [30]. This ambiguity is hopefully further evaluated for possible therapy against osteoporosis along with toxic influence needs to be further verified to exploit its clinical utilization.

2. The anatomical basis: terminology, discovery, new developmental aspects

2.1. Terminology and location

The most recently published international Terminologia Histologica [31] has recommended naming the thyroid follicle's epithelial components T thyrocytes or follicular cells. Adjacent to these follicle cells are pale-wedged shaped cells. In human samples, these cells are few, often isolated or paired within the same epithelial lining, named C thyrocytes, C cells or parafollicular cells. These C cells encompass the same gland's epithelium but typically are prevented by T thyrocytes' junctional complexes to reach the follicles' lumina while their secretory apices discharge CT and small quantities of other peptides such as serotonin, thyrotropin-releasing hormone [7,8] as well as somatostatin [32–39] associated with the *Calcitonin-Gene Related Peptide/Calcitonin* (*CGRP/CT*) gene products as in the circulatory system via fenestrated capillaries located near the basal aspects of the thyroid follicles and with facilitated paracrine diffusion or through undefined, intercellular contacts as shown in rodents [24,32–37,39]. In rabbit [38], like in rat [39], a unique co-localization of CT with somatostatin or somatostatin-like peptide was also demonstrated. In addition, more C cells are in the right lobe than the left thyroid lobe and none in the isthmus [40].

2.2. Discovery

Hazard [41] recalled the detection of the C thyrocytes or C cells in 1875 by E Creswell Baber [42] in dog thyroid glands and named them 'parenchymatous cells'. The C thyrocytes were also recognized in the thyroid gland follicles by many authors [e.g. out of [41]]: 'parafollicular cells' [43–45], 'macrothyrocytes' [46], 'interfollicular cells' [47], 'neurohormonal cells' [48], 'giant-light cells' [49], 'argyrophil cells' [50,51], 'light cell' [52] and, surprisingly,

'mitochondrion-rich cell' (Hürthle cell?) [53]. Normal C cells' histology, histochemistry and ultrastructural aspects can be read along with many publications dealing with the thyroid structure, some are old, very interesting when accessible often with high cost [for example, in Refs. [54–96]]. It is unfortunate that a very large number of publications describing the microscopic anatomy of human and animal C cells are currently considered as archives in most large libraries and in biomedical citation sites because many of these pioneered ultrastructural studies date from the 1960s'. Their content is often available as titles in those sites and eventually only available at high cost for today's investigators. The frustration about these unreadable archives is that significant information become ignored by new investigators or considered 'archaic' even though they could comfort other current data. Similar studies done in the past with ultrastructure aspects must ignominiously recommence, in animals and human samples, at cost of people's efforts and grants of research agencies or charities.

2.3. Newly found developmental origin and histology of the C thyrocytes

Today many textbooks still proclaim that C cells derived from Amine Precursor Uptake and Decarboxylase (APUD) aka Diffuse Neuroendocrine System (DNES) cells [97–101]. These cells were thought to arise from the mesectodermal neural crest [102–104] which then settle the T thyrocytes within the same basal lamina. Using immunohistochemistry with molecular markers along with a detailed morphologic thyroid development and his broad basis of data obtained throughout his career on the thyroid tissues, Kameda and collaborators [105–110] demonstrated in murine and other mammals that not only C thyrocytes but also T thyrocytes and thymus would derive from the ultimobranchial anlage, out of the pharyngeal endoderm lineage and producing, among others, chromogranin A, CGRP, somatostatin along with CT. These endodermal precursor cells required, among others, the transcription factors and signaling molecules Pax9, Tbx1, Ripply3, Pbx1, Mash1 (Ascl1), Hes1, Nkk2.1 (TTF-1), Pax3, Shh, FRS2α, Eya1, EphA4, Hox3 paralogs (Hoxa3, Hoxb3, Hoxd3), Pax8. Others already found that *Eya1* gene is needed to differentiate into functional C cells [111]. Without specific molecular markers C cells' origin was also evoked by others [32,33,112–114] with the possibility evolving into different subtypes in normal development or interactive paracrine and endocrine influences [32,33,38,40,93,113–115] as noted in Ref. [24]. The influence of the pituitary on C cells has already been assumed in one old reference [116]. In addition, with somatostatin [38,40,93] another publication indicated that sympathetic activity can modify their activity [117].

While teaching human microscopic anatomy to students, it has always been intriguing to note that C thyrocytes were scarce among the thyroid follicles, contrarily to most small mammals that displayed many C cells taking residence within the thyroid follicles' epithelia. In some cases, their population appears large enough to become as replacing part of the interstitial, loose connective tissue adjacent to the follicles. Histometry and non-equal distribution among the twin lobes of the thyroid gland have been studied [40,118–121]. A recent review (without text access) seems to confirm Kameda's group and others, cited above, however without study of the migration and interactions with connective and nerve tissues [122].

Extracted from Ref. [24] on can illustrate this large population of C thyrocytes in Zucker rats as found in the FA/? (Fig. 1) less abundant than in the *fa/fa* thyroid (Fig. 2 a–b) as recently studied compared with those found in dog (Fig. 3) and in human thyroids (Fig. 4) [123]. One can recall that *fa/fa* rats carry a leptin receptor homozygous defect associated with a complex metabolic syndrome that favors obesity caused by non-insulin dependent diabetes mellitus and hypothyroidism in which crinophagy was discovered in both C and T thyrocytes [24]. Furthermore, other undetermined cell types were noted aggregated with the typical C cells in these obese rats.

These observations can comfort much earlier data that showed a significant reduction of CT expression and serum release in the obese rats [124–127]. These obese rats develop reproductive deficiency but can survive by some unclear homeostatic balance bearing near toxic, high serum calcium levels [123–133] while assuming, as reported, a typical aging bone structure [124]. In addition, eluded in Ref. [24] as reviewed in diverse mammals, including human, where some functional interdependence between both C and T thyrocytes are reported [32,34,35,93,134–137]. Somatostatin can similarly modulate CT as, for example, insulin-growth factors and thyroid hormone [32,34,36–39,133]. Thus, interactions between C and T thyrocytes can also be suspected with connective tissue cells and innervation [93,138].

Incidentally, this survey on functions of CT in human was originally stimulated by this unpredicted, bizarre physiology found in the obese rodents because if calcium receptors are found on the C cells, these cells seem deficient in the leptin mutated *fa/fa* rats as noted in Ref. [24].

3. Calcitonin production

The human C thyrocytes produce the alpha-calcitonin gene that encodes a small family of peptides that include calcitonin (CT), katacalcin and calcitonin-gene related peptide (CGRP). Both CT and katacalcin peptides are produced from one precursor along with CGRP from the alternative splicing of the *CGRP/CT* gene located on human chromosome 11, that brings either alpha and beta CGRP isoforms, categorized as neuropeptides [35–37,137]. The regulation of *CT* gene expression and activities has already been studied in the peculiar obese Zucker rats [128–130]. CT half-life is quite short and level varies with age and sex [139–143], per thyroid damage or excision [145–148].

4. Calcitonin physiology

The following paragraphs are to note that most data about CT seems to indicate that this hormone alone, with interrelated ectopic one – possibly along with some of the co-secreted superfamily of CT and sex steroids with calcium-rich food intake - antagonizes parathyroid hormone (PTH) activities. CT is regulating a normal calcemia through maintenance of bone mineralization, and preventing its depletion like in osteolysis which results in calcium release in serum that can be balanced by capture of calcium from nutrients as well as retrieving phosphate in vivo and in vitro. Altogether, these activities make a valuable, significant physiologic role in skeletal homeostasis during the entire mammal's life cycle, especially when dynamic bone remodeling occurs during pregnancy and lactation. However, due to some overall decreased actions or of their receptors and intracellular messengers, CT and hormone co-adjuvants (superfamily, estrogens, etc) are unable to prevent the progressive decay favoring osteoporosis or other pathologies. Indeed, in normal physiology, CT stimulates the production of calcitriol or 1, 25-dihydroxycholecalciferol (1, 25(OH) 2D) after calcidiol is transported to the proximal tubules of the kidneys where it is hydroxylated at the 1-α position. The enzyme 25-hydroxyvitamin D3 1-alpha-hydroxylase catalyzes the conversion of calcidiol into calcitriol, the active hormonally active metabolite as vitamin D. Activation of the ligand of the vitamin receptor enhances the level of calcium (Ca^{2+}) in the blood by increasing the uptake of calcium from the gut into the blood.

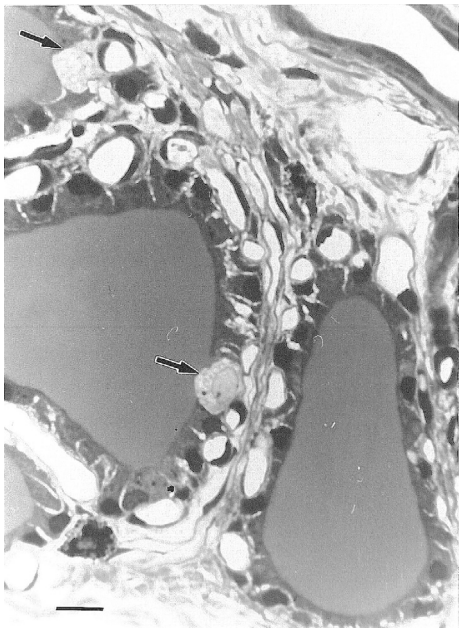

Fig. 1. One-μm thick section of lean (Fa/?) young male Zucker rat thyroid; toluidine blue stain. A well-contrasted, simple cuboidal epithelium lines the follicles and, amongst them, a few poorly contrasted clusters of C cells are easily recognized (arrows). Note the numerous capillaries dilated but empty due to the perfusion. Scale is 10 μm.

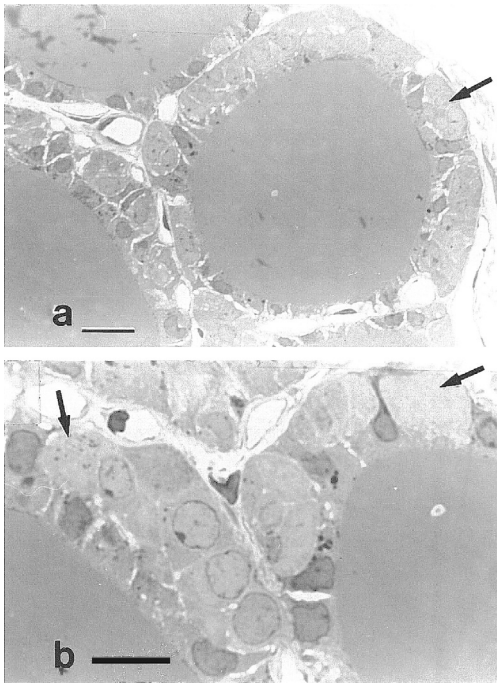

Fig. 2. A–B: One-μm thick sections of obese (fa/fa) young male Zucker rat thyroid; toluidine blue stain. Both A and B micrographs illustrate the abundance of C cells surrounding the thyroid follicles compared with the lean thyroids. The well-contrasted T thyrocytes (T) appear distorted by the swollen, poorly used colloid of the follicles and by their surrounded crowds of parafollicular or C cells that show less stained. Many C cells appear with small and blue dark variable sized granulations and organize as if cell layers are in arcuate rows (arrows) under the stretched follicular cells also containing accumulated dark granulations. The vascular component appears poorly represented around these follicles when compared to those viewed lean rats. Scales equal 10 μm [out of 24].

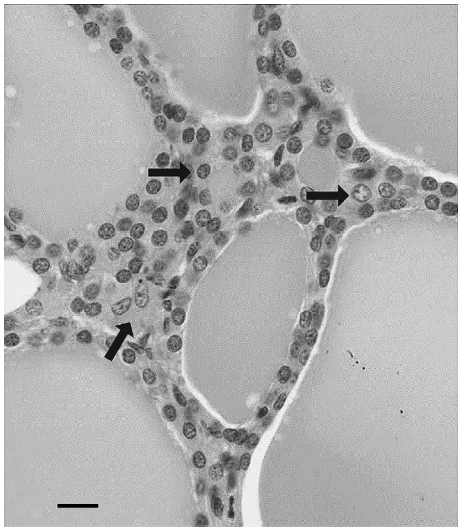

Fig. 3. Five μm thick paraffin section of a dog thyroid, stained by H&E with Saffron C cells are indicated by arrows.

Calcitriol level also augments during pregnancy and lactation. Through their receptors, CT main function appears to control the inhibition of the osteoclasts' activity with the consequence of lowering the serum calcium level [1,5,13,145–148] even though CT half-life and signaling is somewhat short as opposed to that of PTH.

5. CT and human growth and ageing

5.1. Fetal

Building a bone skeleton already suggests that during the fetal and early postnatal periods a likely transient increased population of C thyrocytes with abundant secretion occurs mainly until some late adolescent age while ossification and maturation of the bone skeleton attained its greatest extent, then this cell population

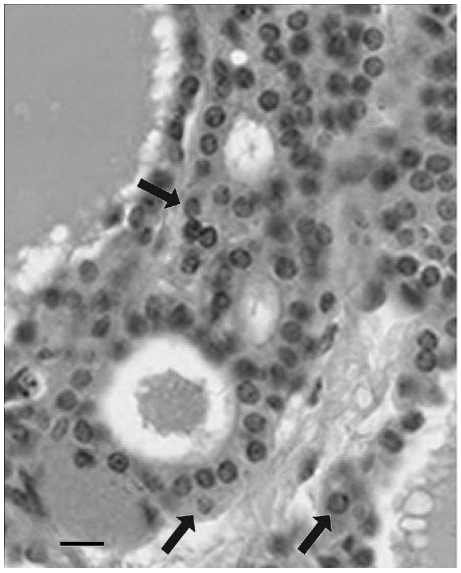

Fig. 4. Five μm thick paraffin section of a human thyroid, stained by H & E with Saffron. Both 3 and 4 scales equal 10 μm and kindly obtained from an area of the digital microscope histology set www.histology.be of the University of Namur Medical School C cells are indicated by arrows.

would probably decrease unless pathology occurs. Overall, one can note the absence of any morphologic correlations in human longitudinal studies that ultimately would correlate with the obvious, less invasive physiologic studies. Kameda and collaborators showed that both C thyrocytes and T thyrocytes derived from the ultimobranchial pharyngeal endoderm lineage and can produce somatostatin along with CT as well as other paracrine or co-localized hormones. This somatostatin production appears transiently in the murine fetus and gradually decreases with age, also in other mammals [107–110]. However, other studies have indicated somatostatin production postnatally and throughout life [32–34,37–39,134–137].

Kovacs and others [149–151] indicated that, pregnancy elevates serum CT and fetal CT level is higher than maternal levels in utero. They also wrote that ' … apart from responding appropriately to changes in the serum calcium concentration, little evidence of an essential role for CT in fetal mineral homeostasis can be found'. Altogether one can suggests that the increased CT with sex steroids, prolactin, placental lactogen and IGF-1 (as well as other unknown factors) associate each other's activity in a sort of ballet where each hormone/dancer accomplishes a choreographic figure that is well defined (but not known entirely) and, in the course of each arabesque, interacts with some or all of the other hormones/components in a performance that results in the increased absorption of calcium by intestines, kidneys and from the skeletal system progressive bone mineralization as early as two-months in-utero. Biopsies demonstrated osteoclastic activity occurring as early as 10-week gestation while bone mass density studies did not adequately describe this physiological axis in-utero [149–151]. However, they also indicated that acute changes in bone mineralization during pregnancy do not seem to cause long-term changes in skeletal calcium content. One would here interpret that this bone remodeling can be viewed to accommodate dynamic developmental changes while increasing bone mineralization occurs in the growing skeletal tissues. As scant as the data are, only a few significant in vitro observations with human fetal tissues and trans iliac crest biopsies verified that CT has anti-osteoclastic activity [152,153].

5.2. Peri- and postnatal

In several readings [149–152,154] one noted that ' … In humans, 1, 25(OH) 2D rises to adult levels over the first 48 h of postnatal life, likely in response to the rise in parathyroid hormone (PTH). Serum CT rises 2- to 10-fold over cord blood levels over the same time interval and then gradually declines. However, ' … in infants that are premature, often develop hypocalcemia along with asphyxia and need extracorporeal oxygenation (or ECMO). These 'premies' can develop seizures [149–151,154,155] because the loss of placental regulation and other defects, including maternal diabetes and hypomagnesemia with high perinatal CT [150]. Consequently, hypercalcitoninemia has been suggested to cause neonatal hypocalcemia. However, other studies indicate that the postnatal rise in CT levels does not correlate to the fall in serum calcium [152–154]. In addition, these premature babies could eventually maintain fetal pulmonary neuroepithelial bodies with secretions that perturb homeostatic calcemia [156]. The same authors indicated that about '6-week postpartum, CT level returns to normal level' [151,154,155]. Reports in veterinary investigations seem to comfort human data [157,158]. In some cases, hyperparathyroidism and pseudohypoparathyroidism require increased calcitriol in view of absent PTH [151,154,155]. Finally, it is noted that ' … mice lacking CT gene lose twice the normal amount of bone mass calcium during lactation'. Thus, CT physiological action seems to protect against an excessive bone mineral resorption during that life period [159–162]. It is well-noted by the same authors [152,161–163]:' … whether CT plays a similar role in human physiology is unknown' but most of these important physiologic data are unfortunately without morphologic support in humans.

5.3. Calcitonin's effect on bone tissue is age and sex dependent

In adolescents, whether male or female, serum CT decreases with age [139–146,164–167]. However, CT maintains a higher level in male than females, especially during postmenopausal ages. There is a similar difference after a hypercalcemic challenge where the response in males is more significant than in females [139,142,168,169].

Through its receptors, and from a few critical data in vitro [81,146,154], CT's main function again appears to control the inhibition of the osteoclasts' activity or formation out of stem monoblasts in the marrow with the resulting, general effect of lowering the serum calcium and phosphate levels [1,5,13,81,170] even though CT half-life is somewhat short [18,145,146,159].

If most biochemical or clinical measurements are sporadically available since long ago from aged humans, one had no opportunities obtaining some published morphologic reports dealing with normal human aging C cells [e.g. Refs. [66,67]] but only old animals.

The hypo calcemic effect of CT - along with CGRP - in mature animals is minimal against osteopenia [169, 170] like CT null mice [171–174]. Calcitriol or vitamin D receptors also inhibits the release of CT as noted in cats [175], thus reducing blood calcium primarily by inhibiting calcium release from bone [176] while the effect of CT on renal excretion is disputed and response is age-dependent unless an active osteolytic bone disease is present [166–168,177].

The major effect of menopause on the skeletal bone mass is a dominant increase in bone turnover with resorption. This may be contributed by both the reduction of intestinal and renal absorption of calcium, hence the body is more prone to fracture. It is more frequent in women than men, probably caused by the decreased anabolic actions of estrogens, thyroxin and other bone growth factors on osteoblasts or their hormonal desensitization as osteoporosis sets [166,167], reviewed in Ref. [168]. In a few clinical studies, a prolonged recovery time for CT out of induced hypercalcemia in longer during ageing [e.g. Ref. [169]]. Furthermore, the mean basal CT level in women is generally lower than that of men. The infusion of calcium or pentagastrin in women resulted in a minimal or undetectable response in plasma CT whereas men showed a significantly greater increase. This relative deficiency in women may likely predispose them to an increase in osteoclast activity and bone loss, especially after menopause through low CT in osteoporosis [166–168].

5.4. Calcitonin is not solo player but performs with others members of the same family

The CT family members are small peptide hormones, involved in calcium homeostasis, vertebrate osteogenesis and osteoblast function [178]. In mammals, six CT family member peptides have been identified, which include calcitonin gene-related peptide alpha and beta (αCGRP and βCGRP), amylin, adrenomedullin 1 (ADM1), adrenomedullin 2 (ADM2 or intermedin) and calcitonin receptor-stimulating peptide (CRSP) [178,179] with distinct effects on bone cells. Calcitonin superfamily also encompasses amylin, calcitonin gene-related peptide, and adrenomedullin [180,181]. There are 2 types of receptors for CT, one for the CT (type I) and another for the sCT (type II). Even though type II provide a CT preferred conformation, type I requires other activity-modifying proteins [182–185].

Whether in conjunction with calcium and phosphate homeostasis, the distribution of CT receptors – along with the CT ectopic sites -

along with the interactions of CT superfamily of hormones, throughout the body of mammals and human is vast, puzzling, and still in need of further clarifications. Morphologic investigations and the support of newest molecular tools should further allow exciting discoveries that can still be made in endocrine studies. Let us mention as examples the CT receptors detected among diverse tissues and organs: bone marrow osteocytes [152,171,173,180,181,186–188], lymphocytes [189], central nervous system and pituitary [190], GI tract (especially stomach oxyntic and G cells and pathology [191–194], kidney [177,195,196], lung [156,197,198] and heart [199–201].

Taking a specific example in relationship with what is stated in the former paragraph, an intramuscular CT injection interferes to decrease gastrin production in old patients (60 and 82 years of age). One could also question: is it only the stomach and intestinal gastrin without the gastrin made in the central nervous system? [see Ref. [230]]. In addition, large doses of pentagastrin or glucagon have been shown to stimulate CT secretion but only cause a slight increase in plasma CT in comparison to calcium infusion. However, the relationship between gastrin and CT has yet to be identified and but it could be ectopic in cases of peptic defects [192,194].

CT receptor diversity and its association to cancers can be of diagnostic but also complicated by its ectopic sources [156,178]. One can think at the recent discovery about the endodermal origin of the C cells [110]. This basic find alone could reshuffle studies about CT paracrine and endocrine interrelationships with thyroid and other hormones.

Looking back in some comparative endocrine reports [202], one cannot ignore some apparent contradictory function of CT on calcemia homeostasis that has been published long ago: CT does not directly alter calcium metabolism in thyroidectomized pigs [203]. In rodents, a meal results in a reduced PTH secretion due to calcium entry via absorption in the digestive tract [204,205] or antibodies against CT comforted those data [206]. Other observations in hypocalcemia and hypothyroidism do not necessarily assist in understanding CT functions [207,208] because C cells metabolic interactions have been reported with T thyrocytes in many mammals and even human thyroid [24,32,33,108,110]. Curiously, extrathyroidal tissues producing CT, found long ago [109,111,112], then detected in humans and monkeys [209–212] have not been granted more recent investigations using combined morphology and molecular tools, including ultrastructure to further understand these intriguing structures.

6. CT and gravity

Long duration of spaceflights with hypo gravity could have deleterious osteoclastic actions [213], in part caused by atrophy or loss of C cells during hypo gravity and, strangely, also caused by hyper gravity [214]. In the meantime, some sort of protection seems possible through the secretion of an inducible 18-kDa heparin-binding cytokine, namely pleiotrophin, also a platelet-derived growth factor [215–217]. Following the changes causing bone demineralization, then a recovery period to reconstruct the bone matrix lasting several weeks is needed [218].

7. CT measurement through its precursor peptide pro-calcitonin (proCT)

In clinical laboratories, diverse methods evolved with advances in technologies to evaluate CT plasma and urine level [219,228]. Early data displayed variability due to product degradation or technical procedures among laboratories [177,180,219,220]. Later, normal and cancer patients CT can be found as monomer and dimer forms in both body fluids as well as the presence of pro-calcitonin (proCT) [185,221–224].

Incidentally, patients who underwent thyroidectomy have been found to have detectable CT in both serum and urine. These observations suggest that human CT can be secreted by extrathyroidal tissues [209–212,225] as it can be found in some bronchial tumors bearing 'carcinoid' cells [156,197,209,210,224]. Similarly, the detection out of lung, thymus and other tissues [109,225] could explain an alteration in the human interpretation of clinical results [210–215]. Furthermore, these ectopic CT data cannot be surprising since one again should recall the endodermal origin of the C cells [107–110]; these should help understanding some of these results [196,202–212,225]. High CT and receptors can be found in some forms of inflammations, especially highly toxic sepsis [225–229] and cancers, e, g. thyroid and medullary tumors [224,230,240–255], ovary [231–235] and prostate [236,237].

Innovative tests have been devised by Trimboli and collaborators in measuring the precursor of CT, pro-calcitonin (proCT), instead of CT and to be less laborious and sensitive technique, indicative of pathophysiologic disorders [237–239]. In all, fine needle aspiration (FNA) technique [228,238–240] is consistent with measurements of the fluidic samples for CT or, likely proCT. Difficult clinical cases can be resolved with imaging as technetium scintigraphy, PET and other combined methodologies, preceding or after surgical intervention [238].

8. Medullary thyroid carcinoma (MTC) and other CT defects

When high CT serum concentration is routinely measured in patients, it is mostly caused by a medullary thyroid carcinoma (MTC) [147,220,228–252]. This type of tumor does cause hypocalcaemia and some of the clinical symptoms include flushing, diarrhea, and/or weight loss.

Although serum CT concentration is being used to diagnose MTC, it is a sensitive test but not a specific marker because other pathologies than MTC, such as neuroendocrine tumors and hypergastrinemia, can also result in high basal CT levels, as noted in several previous paragraphs. For uncommon clinical cases, CT-negative MTC, it has been recommended to perform an ultrasound evaluation of the cervical region and calcium stimulus with measurements using electroluminescence immunoassay (ECLIA) for the follow-up of such cases [228,238,252].

Deficiency of CT is rare and occurs after total excision of the thyroid in some MCT, then serum CT level obviously disappears [147,210] (if no ectopic sources) proving again that CT is essentially produced by C cells.

Finally, in both female and male patients, serum CT can be found elevated in progression along with malignant ovarian [231–235] and prostate cancer [236,237] as a response to high calcemia.

9. Chronic kidney disease (CDK) and calcitonin

CDK is characterized by a loss of renal functions over a long period and results in inability to excrete wastes, to reabsorb minerals, and to form calcitriol. This insufficiency of calcitriol, with hypocalcemia and hyperphosphatemia, causes an increase in PTH synthesis and secretion [253,254]. Renal failure can often result in local parathyroid hypertrophy, cysts or benign parathyroid carcinomas. Thus, in patients with CKD, this secondary hyperparathyroidism with high serum PTH level causes an imbalance in the homeostatic mechanisms controlling bone minerals eventually leading to renal osteodystrophy [255]. CT does not seem to play a protective role in these patients and stay at normal serum level despite the high levels PTH. Hence, does CT protect the body from excessive PTH activity or would this alteration

balanced by nutrients?

10. Calcitonin as a therapeutic agent

10.1. Calcemia

There is little doubt that CT can balance calcemia through internal secretions especially in regards of acute or malignant hypercalcemia [148,256,257] but does not appear to act while osteopetrosis is developed [258].

10.2. Osteoporosis

Out of the original discovery, natural sources have been searched for it to be applied therapeutically against osteoporosis [259–262]. Testing slaughtered fowl and out of fisheries, salmon, extracted salmon CT (sCT) was found to be best source and more active [1,14,20–23] to help maintain bony skeleton while osteoporosis develops [263–272]. The fish sCT either oral or spray seems adequate clinically for managing acute hypercalcemia in patients but its effect lasts only for a week, longer than human CT for its favorable pharmaceutical properties [263–273]. A series of ongoing studies started in 2008 showed sCT taken orally by day seems favorable against osteoporosis or osteoarthritis defects [262–271]. However, new data are developed while this survey is written and submitted to this journal.

10.3. Orthopedic or bone-related defects

Other osteopathic defects have been experimented with sCT to treat vertebral fractures [274,275], pertrochanteric or other bone fractures [276,277]. In addition to the management of lumbar spinal stenosis (LSS) [278,279]. Insofar multiple studies have shown that sCT reduces pain caused by osteoporotic vertebral compression fractures, bone metastases, Paget's disease of bone [256] and adolescent idiopathic scoliosis [280].

Several researchers evaluated the effect of salmon CT using the visual analogue scale (VAS) in patients who suffer from lumbar spinal stenosis (LSS). One of the studies concluded that intramuscular injection of low dose CT on patients with LSS does improve bone pain in patients suffering from severe low back pain but has no effect on walking distance [279]. Another group investigated the effect of sCT as a therapeutic agent to alleviate anastrozole-induced bone pain in patients who suffer breast cancer – they found CT can act as an analgesic and effective to reduce bone pain; they also reported it had no effect on bone loss during cancer treatment [281] or bone pain associated with diabetes [282].

10.4. Low calcemia and ECMO

In case of hypocalcemia the adjustments made in critical illness calls for intravenous calcium [283–285], no mention is made about CT level [284] contrarily with premature infants [149–151,154,155,286,287] when high CT occurs perinatally.

11. Toxic effects of sCT?

CT is most widely used parenterally, however oral and nasal formulations are also available [21–23,262,263]. An isolated study reported an association between sCT use and cancer [29]. However, another recent study claims no carcinogenetic association [30]. This point of contention or ambiguous data should also be reviewed soon considering the ongoing sCT clinical trials [272].

12. Conclusion

The function of CT in humans is to be associated or to control the dynamics of bone growth and its homeostasis during fetal, youth, adulthood and decreased in ageing. It seems to prevail during the periods of high calcium demands dealing with bone remodeling, especially after fractures and the physiologic calcemia needed during lactation. In these instances, some animal studies suggest CT acts on the kidneys to favor an increased production of the active form of vitamin D to help meet the high body calcium demands along with some of the PTH activities by intervening in colonic reabsorption of calcium from the diet instead of using bone minerals as a mineral source. Other influences of paracrine hormones or signaling factors can interact with the C cells where most synthesis and release of CT occurs, including of some ectopic sites, likely lungs and thymus.

Even though a plethora of studies have been made on the human thyroid in basic and clinical investigations and some aspects of C cells and CT physiology remain a puzzle [27,28] The newly discovered common endodermal origin from the ultimobranchial body of the C and T thyrocytes (and other associated cells that probably disappear in fetus or soon after birth in human) may induce some studies. Especially new C cells' developmental and longitudinal human research studies to be done, first noninvasive, such as fluid measurements. In addition, morphology and molecular techniques added to ethical cadaveric studies would improve the understanding of ageing aspects about those C cells regarding the thyroid gland and the etiology of rare pathologies to foreseen new therapeutic strategies.

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