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Calcitonin Gene Peptides: The Diagnostic Value of Measurement in Medullary Thyroid Carcinoma

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Calcitonin Gene Peptides: The Diagnostic Value of Measurement in Medullary Thyroid Carcinoma

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The calcitonin gene encodes a family of peptides, at least three of which normally circulate in man: calcitonin (CT), a calcium-lowering hormone; katalcalcin (KC), a peptide of unknown function; and calcitonin gene-related peptide (CGRP), a neuropeptide and potent vasodilator. In a study of 45 patients with medullary thyroid carcinoma (MTC), plasma CGRP was elevated in approximately 50% of cases. Furthermore, CGRP levels did not correlate with CT levels. However, plasma KC was elevated in all cases, with a good correlation with CT levels, as has been noted previously. Measurement of CT or KC appears to be superior to measurement of CGRP for the detection of MTC. (Henry Ford Hosp Med J 1987;35:118-9)

An overview of three products of the human calcitonin gene is presented here with particular reference to the diagnostic value of their measurement in medullary thyroid carcinoma (MTC).

Calcitonin

The recognition of calcitonin (CT) as a tumor marker for MTC was the product of a sequence of exciting contributions made by scientists working in various disciplines of medical science. Following the discovery of a calcium-lowering factor, "calcitonin," by Copp and Cheney (1) who believed CT to be of parathyroid origin, further studies demonstrated the thyroid origin of this factor (2,3). In 1964, Foster et al (4) identified the parafollicular cells of the thyroid gland as the source of CT, and the term "C-cells" (C for calcitonin) was introduced by Pearse (5). Later, Williams suggested that MTC is a tumor of the parafollicular cells (6). This suggestion proved correct as two important developments followed: 1) the isolation and characterization of CT from a single MTC tumor (7), and 2) the demonstration of high levels of CT (measured in bioassay) in the plasma of patients with MTC (8,9) in whom calcium (Ca) infusion produced a further increase in CT levels.

The characterization of human CT in 1968 (10) was followed in the same year by its synthesis (11). This, together with advances in radioimmunoassay (RIA) techniques, has permitted the development of a specific RIA for human CT in various laboratories (12,13).

MTC is now classically diagnosed by the detection of high levels of immunoreactive CT in plasma. In patients with C-cell hyperplasia in whom basal CT levels are normal, the diagnosis can be made by observing an exaggerated response to stimulation of release by either Ca, pentagastrin, or alcohol (13-16), or a combination of Ca and pentagastrin.

Katalcalcin or PDN-21

The complete sequence of the human CT precursor has been predicted by cloning and analysis of recombinant DNA from messenger RNA extracted from human MTC (17,18). This revealed that CT is flanked on its carboxy-terminus by a 21 amino acid peptide and on its amino-terminus by a larger peptide of 82 amino acids.

When the carboxy-terminus peptide (PDN-21) was synthesized, it was thought initially to have a Ca-lowering activity; hence the introduction of the name katalcalcin (KC) (19). However, it is now clear that KC has no Ca-lowering activity, and its function, if any, is not yet known. Using specific RIA, KC is shown to circulate at high levels in patients with MTC (19-21) and at approximately equimolar amounts with CT. Furthermore, KC release responds to the same stimuli as CT (19-21). Therefore, diagnostically, KC is as good a marker as CT for the detection of MTC and C-cell hyperplasia.

Calcitonin Gene-Related Peptide

The CT gene encodes the precursor of another peptide, calcitonin gene-related peptide (CGRP). This peptide was predicted on the basis of nucleotide sequence data from the rat (22) and was thought to arise from differential tissue-specific processing of the transcript from the rat CT gene. Its existence in the rat was suggested by immunofluorescent localization (23), and it was shown to be widely distributed in the central nervous system.

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We have isolated and characterized a related peptide from human MTC tumor (h-CGRP) (24). CGRP has been shown to be the most potent vasodilator yet discovered (25,26). Recently, we have shown that immunoreactive CGRP normally circulates in humans in higher concentrations than immunoreactive CT (27).

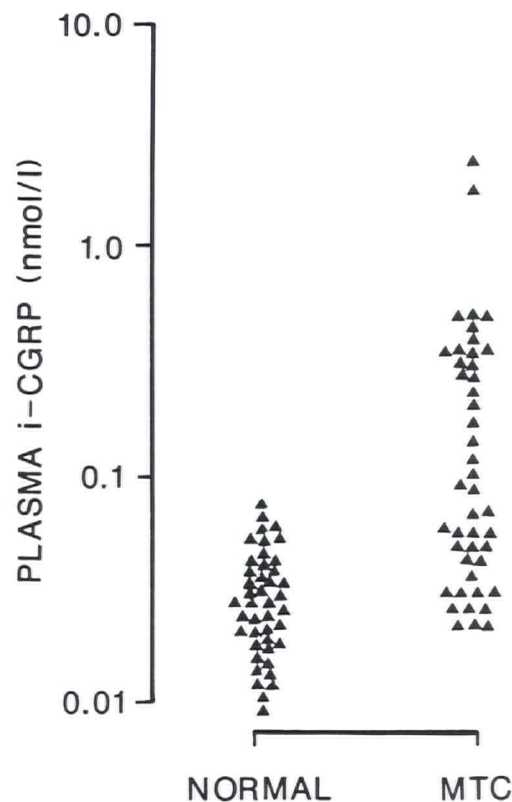
More recently we have studied the circulating levels of CGRP, together with CT and KC, in 45 patients with MTC. Plasma CGRP was elevated in approximately 50% of cases (Figure). There was a weak correlation between CGRP levels and either CT or KC levels. However, plasma CT and KC were elevated in all cases and circulated in equimolar amounts. Their levels were approximately tenfold higher than those of CGRP. We have concluded that CGRP is not a sensitive marker for MTC, and measurement of CT or KC is superior to measurement of CGRP for the detection of MTC.

Acknowledgments

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Figure—Plasma levels of immunoreactive CGRP in 45 patients with MTC and in normal controls.

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