Endokrynologia Polska/Polish Journal of Endocrinology
Tom/Volume 61; Numer/Number 4/2010
ISSN 0423–104X

Chromogranin A (CgA) — the influence of various factors *in vivo* and *in vitro*, and existing disorders on it's concentration in blood

Chromogranina A (CgA) — wpływ różnych czynników *in vivo*, *in vitro* i istniejących chorób na jej stężenia we krwi

Piotr Glinicki, Wojciech Jeske

Department of Endocrinology, The Medical Centre of Postgraduate Education, Warsaw, Poland

Abstract

Chromogranin A (CgA) is regarded as a major, nonspecific neuroendocrine tumour (NET) marker. The results of CgA blood concentration, however, may actually be influenced by various factors or coexisting pathological conditions. Among the factors causing a substantial increase of the blood CgA concentration are: treatment with proton-pump inhibitors or H_2 -receptor blockers, chronic atrophic gastritis (type A), impaired renal function, prostate cancer and BPH, and rheumatoid arthritis with high level of RF IgM. In addition, the sort of investigated biological material (whether it is serum or plasma) is of importance.

There are also many conditions which may have a moderate or little influence on the concentration of CgA, among them are: inflammatory bowel disease (ulcerative colitis and Crohn's disease), deteriorating liver function, untreated essential hypertension, heart failure, hypercortisolism, pregnancy, and, in some subjects, ingestion of a meal.

Proper assessment of the CgA results requires detailed knowledge about various factors, drugs, and pathological conditions influencing its concentration in blood. **(Pol J Endocrinol 2010; 61 (4): 384–387)**

Key words: *chromogranin A, neuroendocrine tumours*

Streszczenie

Chromogranina A (CgA, *chromogranin A*) jest obecnie uznana jako główny, niespecyficzny marker guzów neuroendokrynnych (NET, *neuroendocrine tumours*). Liczne czynniki i stany patologiczne mogą wpływać na stężenie CgA. Wśród czynników powodujących największy wzrost stężenia CgA wymienić należy: leki z grupy inhibitorów pompy protonowej i antagonistów receptorów H_2, zaś spośród różnych patologii: przewlekłe zanikowe zapalenie błony śluzowej żołądka typu A (*atrophic gastritis*), postępująca niewydolność nerek, rak i przerost prostaty. Wpływ na wynik oznaczenia CgA ma także rodzaj użytego materiału biologicznego (czy jest to surowica czy osocze) oraz na przykład obecność czynnika reumatoidalnego (RF) w klasie IgM.

Istnieje również wiele czynników i stanów patologicznych, które mają umiarkowany lub niewielki wpływ na stężenie CgA, wśród nich wymienia się: choroby zapalne jelit (wrzodziejące zapalenie jelita grubego, choroba Leśniowskiego-Crohna), niewydolność wątroby, niewydolność serca, nieleczone nadciśnienie tętnicze, hiperkortyzolemia, ciąża oraz, u niektórych pacjentów, wcześniejsze spożycie posiłku. Dla prawidłowej interpretacji oznaczeń CgA niezbędna jest dobra znajomość potencjalnego wpływu na jej stężenie we krwi różnych czynników, stosowanych leków lub współistniejących schorzeń. **(Endokrynol Pol 2010; 61 (4): 384–387)**

Słowa kluczowe: *chromogranina A, guzy neuroendokrynne*

Introduction

Chromogranin A (CgA) is a 49-kDa hydrophilic glycoprotein composed of 439 aa. It is present in all normal and abnormal neuroendocrine cells [1, 2]. The CgA gene is located on the 14th chromosome. CgA is a major Ca^{2+} storage protein and can aggregate at high concentrations of calcium [3]. Chromogranin A belongs to the chromogranin/secretogranin family — acid secretory proteins which are presented in the DES (diffuse endocrine system) in the gastrointestinal tract, respiratory system, and endocrine glands (adrenals, pituitary) and groups of endocrine cells in the glandular tissues such as pancreas and thyroid [4].

The exact role and function of CgA is still unknown. It is suggested that it could exert some intracellular and extracellular functions:

— CgA as a pro-hormone is a precursor of biologically active peptides (vasostatin, pancreastatin, chromo-

Piotr Glinicki M. Sc., Department of Endocrinology, The Medical Centre of Postgraduate Education, Bielanski Hospital, 80 Cegłowska St., 01–809 Warsaw, Poland, tel.: +48 22 56 90 293/168, e-mail: piotr.glinicki@wp.pl

statin) which have autocrine, paracrine, and endocrine functions;
— It plays a role in the production, storage, transport, and regulatory functions of peptide hormones [5-7].

CgA — circulating tumour marker

Chromogranin A is a major, nonspecific NET marker. The expression of CgA depends on the cell type and on the number of secretory granules present in the cells [8]. Chromogranin A is physiologically released by exocytosis and may be detected in blood as a circulating tumour marker. CgA is a universal marker of neuroendocrine tissues and tumours, such as: GEP NET (gastro-entero-pancreatic neuroendocrine tumours), carcinoid, pheochromocytoma, thyroid medullary carcinoma, parathyroid adenoma, MEN 1 syndrome, neuroblastoma, small cell lung cancer, bronchopulmonary NETs, and others [9, 10]. Measurement of CgA levels in blood can also be used for monitoring the progression or regression of neuroendocrine tumors during treatment.

The sensitivity of this tumour marker in NETs fluctuates between 10 and 100% and its specificity between 68 and 100% [10]. In patients with metastatic disease, CgA has a sensitivity of 60–100% and its level may increase even 100–1000 times. The highest values are observed in carcinoid tumours with liver metastases [11]. In small tumours (except gastrinoma) such as: insulinoma, paraganglioma, small bronchi carcinoids, and pituitary tumours, the levels of CgA may be in the normal range. [12]. The highest sensitivity of CgA measurement was noted in gastrinoma (100%), pheochromocytoma (89%), carcinoid tumours (80%), non-functioning tumours of the endocrine pancreas (69%), and medullary thyroid carcinoma (50%) [13], and usually the CgA blood level depends on the size of the tumour and the presence of metastasis [14, 15].

The effect of various pathological conditions or diseases on CgA blood levels

The most common unrecognised cause of increased CgA levels is probably silent atrophic gastritis and gastritis due to *Helicobacter pylori* infection [16, 17].

Chronic elevation of serum gastrin levels in patients with gastritis, especially those treated with proton pump inhibitors, may initiate hyperplasia of the ECL of the stomach. Therefore, measurement of serum CgA could be a useful tool for monitoring ECL cell hyperplasia, which potentially might precede NE cell neoplasia [18–20]. Patients with *Helicobacter pylori*—positive serology—have higher serum gastrin and CgA levels than those with negative serology [21]. In organ dysfunction such as renal and liver failure, the CgA levels in serum or plasma may also be markedly increased. In renal insufficiency, the concentration of CgA may increase systematically, and the highest levels are found in end-stage renal disease [22].

High CgA blood concentrations may also be present in prostate carcinoma and benign prostate hypertrophy (BPH). Plasma CgA levels in prostate cancer increase with the severity of the disease and are associated with a poor survival prognosis [23].

Slightly increased concentrations of CgA have been observed in: ulcerative colitis and Crohn's disease, Parkinson's disease, rheumatoid arthritis, hyperparathyroidism (HPT), hyperthyroidism, in some postmenopausal women (probably due to the increased sympathetic tone), and during pregnancy [17, 24–25].

Severe heart diseases like infarction, heart failure and hypertension associated with an increased sympathetic tone and/or increased secretion of glucocorticoids may also result in elevation of CgA levels [26–28].

The concentration of CgA may be also increased in some patients with: breast cancer, lung cancer, gastrointestinal cancer, uterine cancer, genitourinary cancer, haematological cancer, and head and neck cancer, which are generally not regarded as neuroendocrine tumours [29].

The effect of drugs on the CgA blood level

There are two main groups of drugs: proton pump inhibitors (PPIs) and histamine H_2-receptor blockers (H_2--RAs), which can markedly influence the CgA blood concentration. These drugs are very important in the treatment of the gastro-oesophageal reflux disease, peptic ulcer, and they are widely used for gastric protection during administration of steroids or nonsteroidal anti-inflammatory drugs [30–31].

Inhibition of gastric acid secretion stimulates G cells to produce gastrin. Therefore, long-term treatment with proton pump inhibitors and, to a lesser extent with histamine 2-receptor antagonist, may lead to the development of gastric enterochromaffin-like (ECL) cell hyperplasia [32].

Regarding this very potent effect of PPI on CgA level, administration of this drug, if possible, should be interrupted, leaving a clearance of at least three half-lives, prior to blood sampling (it means in practice around two weeks), or PPI should be temporarily replaced by a H2-blocker for two weeks and the later drug should be discontinued three days before determination of the CgA concentration [21, 33–36].

Treatment with corticosteroids may increase the concentration of CgA by about two times, while most drugs used in the treatment of hypertension have little or no effect on plasma CgA concentration [13].

Table I. *The effect of various pathological conditions and drugs on the CgA blood level*
Tabela I. *Wpływ różnych stanów patologicznych i leków na stężenie CgA we krwi*

High or moderate increase of the blood CgA level	Moderate or little increase of the blood CgA level
— proton-pump inhibitors — histamine H_2 receptor-blockers — chronic atrophic gastritis (type A) — impaired renal function; — RF IgM — some chemiotherapeutic drugs causing nephrotoxic effect or renal failure — prostate cancer and BPH	— inflammatory bowel disease (ulcerative colitis andCrohn's disease) — untreated essential hypertension — acute coronary syndrome — cardiac insufficiency — giant cell arteritis — deteriorating liver function (cirrhosis, chronic hepatitis) — pancreatic adenocarcinoma — irritable bowel syndrome — hepatocellular carcinoma — hyperthyroidism — hyperparathyroidism (HPT) — airway obstruction in smokers — systemic rheumatoid arthritis — Parkinson disease — pregnancy — non-endocrine tumours (breast cancer lung cancer, gastrointestinal cancer, uterine cancer, genitourinary cancer, haematological cancer, head and neck cancer)

During chemotherapy of NE tumours (e.g. with the use of streptozotocin), the levels of CgA may increase even if the tumour mass shrinks, which may be due to the release of CgA from the damaged tissue or due to the nephrotoxic effect of such drugs [37].

Some other *in vivo* and *in vitro* factors having a potential influence on the measurement of CgA blood level

CgA is a relatively stable protein. Biological material (serum, plasma) can be stored at –20°C for a long time. Few cycles of thawing and refreezing of samples does not damage the molecule [38]. Circulating CgA is present in healthy subjects, and the values obtained are not dependent on age and sex [39,40]; only *Tsao* et al. have described higher concentrations of CgA in males than in females, regardless of age [41]. Daily fluctuations of CgA can be approximately 20–25% [42], and the higher levels are observed in the late afternoon and at night [43]. The increase of CgA concentration after exercise is small; it can be seen mainly in patients with essential hypertension [44].

Considering the stability of CgA, it should be remembered, however, that it can aggregate at high concentrations of free Ca^{2+} ions. For this reason, significant differences in the CgA results may be observed depending on the sort of studied biological material, whether it is serum or plasma. We were able to show that CgA levels, measured either by IRMA or ELISA CIS-kits, appeared to be 20–76% higher in plasma than in serum [45].

The CgA levels may be also influenced by ingestion of a meal. A meal can stimulate G and ECL cells of the stomach and cause the release of gastrin and CgA [46]. Such an effect was observed especially in patients who were on long-term treatment with proton pump inhibitors (PPIs) or H_2-RAs. So far, it is not known whether an increase of CgA after meal may also be significant in patients who are not treated with PPIs. For this reason, in all the investigated patients, perhaps blood should be collected in a fasting state [47]. Our preliminary study on a group of healthy subjects and patients has shown that this increase was very small, but in a few cases the difference was about 24–36%.

Some disturbances in the determination of CgA levels in serum or plasma may also be caused by: haemolysis, lipaemia, turbidity of sample, presence of fibrin, and the so-called "effect of imposing" connected with the presence in patients samples of different (auto)antibodies such a: heterofile-Ab, avidine-Ab, or RF-IgM [48].

Conclusions

Biochemical measurements are very important for proper diagnosis, follow up, and for monitoring the effectiveness of the applied treatment. Correct interpreta-

tion of the obtained results requires good knowledge of the analytical factors and associated diseases or pathological conditions which may potentially influence the results of laboratory determinations. In our article we present some updated data on chromogranin A and put special attention to the most important in vivo and in vitro factors which have, or may have, an influence on the measured concentration of CgA (Table I). Discussion of these issues seems important for clinical practice and the proper assessment of obtained CgA results.

References

1. Barakat MT, Meeran K, Bloom S. Neuroendocrine tumours. Endocrine-Related Cancer 2004; 11: 1–18.
2. Payan-Carreira R, Rodrigues P, Carvalho PRF. Chromogranin-A expression in the bovine testis. Anim Repr Sci 2006; 96: 146–153.
3. Yoo AH, You AH, Kang MK et al. Localization of the secretory granule marker protein chromogranin B in the nucleus. J Biol Chem 2002; 277: 16011–16021.
4. Helle KB. The granin family of uniquely acidic proteins of the diffuse neuroendocrine system: comparative and functional aspects. Biol Rev Camb Philos Soc 2004; 79: 769–794.
5. Koshimizu H, Kim T, Cawley NX et al. Chromogranin A: A new proposal for trafficking, processing and induction of granule biogenesis. Regul Pept 2010; 160: 153–159.
6. Taupenot L, Harper KL, O'Connor DT. The chromogranin-secretogranin Family. N Engl J Med 2003; 348: 1134–1149.
7. Inomoto C, Osamura RY. Formation of secretory granules by chromogranins. Med Mol Morphol 2009; 42: 201–203.
8. Klöppel G. Tumour biology and histopathology of neuroendocrine tumours. Best Pract Res Clin Endocrinol Metab 2007; 21: 15–31.
9. Kos-Kudła B, Fołtyn W, Zemczak A et al. Diagnostyka i leczenie guzów neuroendokrynnych żołądkowo-jelitowo-trzustkowych (GEP NET). Przeg Gastroenter 2006; 1: 3–9.
10. Nehar D, Lombard-Bohas C, Olivieri S et al. Interest of chromogranin A for diagnosis and follow-up of endocrine tumours. Clin Endocrinol 2004; 60: 644–652.
11. Kos-Kudła B, Bolanowski M, Handkiewicz-Junak D et al. Diagnostic and therapeutic guidelines for gastrointestinal neuroendocrine tumors (recomended by the Polish Network of Neuroendocrine Tumors). Endokrynol Pol 2008; 59: 41–56.
12. Lorenzo MJV. Neuroendocrine tumors — fascination and infrequency. Rev Esp Enferm Dig 2009; 101: 195–208.
13. Nobels FRE, Kwekkeboom DJ, Bouillon R et al. Chromogranin A: its clinical value as marker of neuroendocrine tumors. Eur J Clin Invest 1998; 28: 431–440.
14. Vinik AI, Silva MP, Woltering G et al. Biochemical testing for neuroendocrine tumors. Pancreas 2009; 38: 876–889.
15. Bilek R, Safarik L, Ciprova V et al. Chromogranin A, a member of neuroendocrine secretory proteins as a selective marker for laboratory diagnosis of pheochromocytoma. Physiol Res 2008; 57: 171–179.
16. Nobels FR, Kwekkeboom DJ, Coopmans et al. Chromogranin A as serum marker for neuroendocrine neoplasia: comparison with neuron-specific enolase and the alpha-subunit of glycoprotein hormones. J Clin Endocrinol Metab. 1997; 82: 2622–2628.
17. Granberg D, Stridsberg M, Seensalu R et al. Plasma chromogranin A in patients with multiple endocrine neoplasia type 1. J Clin Endocrinol Metab 1999; 84: 2712–2717.
18. Kleveland O, Syversen U, Slørdahl KW et.al. Enterochromaffin-like (ECL) cell hyperplasia/neoplasia as a source of chromogranin A (CgA) increase in blood. Digestation 2001; 64: 71–74.
19. Syversen U, Ramstad H, Gamme K et al. Clinical significance of elevated serum chromogranin A levels. Scand J Gastroenterol 2004; 10: 969–973.
20. Peracchi M, Gebbia C, Basilisco D et al. Plasma chromogranin A in patients with autoimmune chronic atrophic gastritis, enterochromaffin-like cell lesions and gastric carcinoids. Eur J Endocrinol 2005; 152: 443–448.
21. Sanduleanu S, Stridsberg M, Jonkers D et al. Serum gastrin and chromogranin A during medium- and long-term acid suppressive therapy: a case-control study. Aliment Pharmacol Ther 1999; 13: 145–153.
22. O'Connor DT, Pandian MR, Carlton E et al. Rapid radioimmunoassay of circulating chromogranin a: in vitro stability, exploration of the neuroendocrine character of neoplasia, and assessment of the effects of organ failure. Clin Chem 1989; 35: 1631–1637.
23. Kadmon D, Thompson TC, Lynch GR et al. Elevated plasma chromogranin-A concentrations in prostatic carcinoma. J Urol 1991; 146: 358–361.
24. O'Toole D, Grossman A, Gross D et al. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: Biochemical Markers. Neuroendocrinology 2009; 90: 194–202.
25. Nobels FRE, Kwekkeboom DJ, Coopmans W et al. A comparison between the diagnostic value of the measurement of gonadotropins, α-subunits and chromogranin A and their response to TRH in clinically non-functioning, α-subunit secreting and gonadotroph pituitary adenoma. J Clin Endocrinol Metab 1993; 77: 784–789.
26. Takiyyuddin MA, Cervenka JH, Hsiao RJ et al. Chromogranin A. Storage and release in hypertension. Hypertension 1990; 15: 237–246.
27. Takiyyuddin MA, Parmer RJ, Kailasam MT et al. Chromogranin A in human hypertension. Hypertension 1995; 26: 213–220.
28. Jansson AM, Røsjø H, Omland T et al. Prognostic value of circulating chromogranin A levels in acute coronary syndromes. Eur Heart J 2009; 30: 25–32.
29. Modlin IM, Gustafsson BI, Moss SF et al. Chromogranin A – biological function and clinical utility in neuro endocrine tumor disease. Ann Surg Oncol 2010; 9 (in print)
30. Czerwionka-Szaflarska M, Brazowski J. Inhibitory pompy protonowej w medycynie wieku rozwojowego. Pol Merk Lek 2007; 128: 154–158.
31. Waldum HL, Syversen U. Serum chromogranin A in the control of patients on long-term treatment with inhibitors of acid secretion. Eur J Clin Invest 2001; 31: 741–743.
32. Kuipers EJ. Proton pump inhibitors and gastric neoplasia. Gut 2006; 55: 1217–1221.
33. Giusti M, Sidoti M, Augeri C et al. Effect of short-term treatment with low dosages of the proton-pump inhibitor omeprazole on serum chromogranin A levels in man. Eur J Endocrinol 2004; 150: 299–303.
34. Waldum HL, Arnestad JS, Brenna E et al. Marked increase in gastric acid secretory capacity after omeprazole treatment. Gut 1996; 39: 649–653.
35. Igaz P, Müllner K, Hargitai B et al. Marked chromogranin A elevation in a patient with bilateral adrenal incidentalomas, and its rapid normalization after discontinuation of proton-pump inhibitor therapy. Clin Endocrinol 2007; 67: 805–808.
36. Stridsberg M, Eriksson B, Fallström et al. Measurements of chromogranin B can serve as a complement to chromogranin A. Regul Pept 2007; 139: 80–83.
37. Lamberts SW, Hofland LJ, Nobels FRE. Neuroendocrine tumor markers. Front Neuroendocrinol 2001; 22: 309–339.
38. Sørhaug S, Langhammer A, Waldum HL et al. Increased serum levels of Chromogranin A in male smokers with airway obstruction. Eur Respir J 2006; 28: 542–548.
39. Dittadi R, Meo S, Gion M. Biological variation of plasma chromogranin A. Clin Chem Lab Med 2004; 42: 109–110.
40. Drivsholm L, Paloheimo LI, Österlind K. Chromogranin A, a significant prognostic factor in small cell lung cancer. Br J Cancer 1999; 81: 667–671.
41. Tsao KC, Wu JT. Development of an ELISA for the detection of serum chromogranin A (CgA) in prostate and non-neuroendocrine carcinomas. Clin Chim Acta 2001; 313: 21–29.
42. Takiyyuddin MA, Neumann HP, Cervenka JH et al. Ultradian variations of chromogranin A in human. Am J Physiol 1991; 261: 939–944.
43. Giampaolo B, Angelica M, Antonio S. Chromogranin „A" in normal subjects, essential hypertensives and adrenalectomized patients. Clin Endocrinol 2002;57: 41–50.
44. Elias AN, Wilson AF, Pandian MR et al. Chromogranin A concentrations in plasma of physically active men after acute exercise. Clin Chem 1992; 38: 2348–2349.
45. Glinicki P, Kapuścińska R, Jeske W. Differences in the concentration of chromogranin A (CgA) in the serum and plasma. Endokrynol Pol 2010; 61: 241 (conference abstract).
46. Sanduleanu S, De Bruïne A, Stridsberg M et al. Serum chromogranin A as a screening test for gastric enterochromaffin-like cell hyperplasia during acid- suppressive therapy. Eur J Clin Invest 2001; 31: 802–811.
47. Frossmark R, Jianu CS, Martinsen TC et al. Serum gastrin and chromogranin A levels in patients with fundic gland polyps caused by long-term proton-pump inhibition. Scan J Gastroenterol 2008; 43: 20–24.
48. Glinicki P, Jeske W. Chromogranin A (CgA) — characteristic of the currently available laboratory methods and conditions which can influence the results. Endokrynol Pol 2009; 60: 415–419.