



# Chromogranin-A and its role in the pathogenesis of diabetes mellitus

## Chromogranina A i jej rola w patogenezie cukrzycy

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### Abstract

Chromogranin A is a member of the granin glycoprotein family that is expressed by the endocrine and neuroendocrine cells of different organs. Intracellularly, chromogranin A contributes to the regulation of secretion and gives several cleavage products after secretion. Some of its cleavage products modify the hormone functions in autocrine and paracrine ways, while the functions of others have not been fully understood yet.

Serum chromogranin A level is most prominently used in neuroendocrine tumour diagnostics. In addition, recent studies have suggested that chromogranin A and some of its cleavage products (pancreastatin and WE-14) also play important roles in the pathogenesis of the various forms of diabetes mellitus, but their exact mechanisms still need to be clarified.

Higher chromogranin A, pancreastatin, and WE-14 levels have been reported in type 1, type 2, and gestational diabetic patients compared to healthy controls. A notable connection has been inferred through the observation that type 1 diabetes mellitus is not at all or rarely developed in chromogranin A gene-knockout, non-obese diabetic model mice compared to non-knockout, non-obese diabetic mice. Pancreastatin inhibits insulin release in various cell and animal models, and WE-14 serves as an autoantigen for both CD4<sup>+</sup> and CD8<sup>+</sup> beta cell-destructive diabetogenic T-cell clones in type 1 diabetes.

Chromogranin A contributes to the pathogenesis of diabetes mellitus according to the available literature. The current findings facilitate further investigation to unravel the deeper relationships between this glycoprotein and diabetes. (*Endokrynol Pol* 2018; 69 (5): 598–610)

**Key words:** chromogranin A, diabetes mellitus, diabetes mellitus type 1, diabetes mellitus type 2, gestational diabetes, mice inbred NOD, pancreastatin, WE-14

### Streszczenie

Chromogranina A jest członkiem rodziny glikoprotein granin i występuje w komórkach endokrynych i neuroendokrynych różnych organów. Chromogranina A wewnątrzkomórkowo przyczynia się do regulacji wydzielania, również tworzą się liczne produkty jej rozkładu po wydzielaniu. Niektóre produkty rozpadu modyfikują funkcje hormonalne w sposób autokryny lub parakryny, a w przypadku innych produktów funkcje te nie są w pełni znane.

Stężenie chromograniny A w surowicy jest używane przede wszystkim w diagnostyce guzów neuroendokrynych. Co więcej, z ostatnich badań wynika, że chromogranina A oraz niektóre jej produkty rozpadu, takie jak pankreostatyna i WE-14, odgrywają istotną rolę w patogenezie różnych form cukrzycy, choć dokładny mechanizm pozostaje do wyjaśnienia.

Wyższe stężenie chromograniny A, pankreostatyny i WE-14 w porównaniu z grupą kontrolną było wykryte u pacjentów z cukrzycą typu 1, 2 oraz cukrzycą ciążową. Na podstawie obserwacji wyciągnięto ważny wniosek, że cukrzyca typu 1 w ogóle nie lub bardzo rzadko rozwija się u nieotyłych, transgenicznych pozbawionych chromograniny A myszy z cukrzycą w porównaniu z niezmutowanymi, nieotyłymi myszami z cukrzycą.

Pankreostatyna hamuje wydzielanie insuliny w różnorodnych modelach komórkowych oraz zwierzęcych, a WE-14 służy jako autoantymogen zarówno dla klonów CD4<sup>+</sup> i CD8<sup>+</sup> limfocytów T niszczących komórki β w cukrzycy typu 1.

Według dostępnej literatury, chromogranina A przyczynia się do patogenezy cukrzycy. Obecne ustalenia motywują do dalszych badań, aby wyjaśnić bardziej ściśle zależności między tą glikoproteiną a cukrzycą. (*Endokrynol Pol* 2018; 69 (5): 598–610)

**Słowa kluczowe:** chromogranina A, cukrzyca, cukrzyca typu 1, cukrzyca typu 2, cukrzyca ciążowa, myszy szczepu NOD, pankreostatyna, WE-14

### Introduction

Diabetes mellitus is a complex metabolic disorder with multifactorial aetiology. It is one of the most prevalent diseases in our time, occurring in approximately 8–9% of the world's population. Its current

classification — recently described by the American Diabetes Association [1] — includes several forms: type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), other specific types (for example genetic defect forms, endocrinopathies, diseases of the exocrine pancreas and drug- or chemical-induced



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**Table I. Comparison of type 1, type 2, and gestational diabetes****Tabela I. Porównanie cukrzycy typu 1, 2 i cukrzycy ciążowej**

	<b>Type 1 diabetes mellitus (T1DM)</b>	<b>Type 2 diabetes mellitus (T2DM)</b>	<b>Gestational diabetes mellitus (GDM)</b>
Prevalence	~10% of the diabetic patients	~90% of the diabetic patients	~14% of the pregnancies
Age at recognition	Usually young	Usually older	Second trimester of the pregnancy
Development (speed, onset)	Fast, acute onset	Slow, usually when a comorbidity is recognised	Only during routine testing
Overweight	Usually no	Often	Often
Insulin response	Insulin deficiency	Insulin resistance	Usually insulin resistance
Family history	Usually rare	Usually diabetes in family	Usually T2DM in family
Pathomechanism	Autoimmune destruction of the pancreatic beta cells	Insulin resistance and later beta cell dysfunction	Insulin resistance caused by hormonal changes of the placenta
Treatment	Insulin	Early diagnosis: diet and change of lifestyle Late diagnosis: oral antidiabetics and/or insulin	First: diet and exercise If treatment targets are not met in 1–2 weeks: insulin
Common comorbidities	Various autoimmune diseases and mental disorders [141]	Obesity, dyslipidaemia, cardiovascular events and hypertension, micro- and macrovascular complications	Mother: Hypertension, pre-eclampsia Foetus: shoulder dystocia, stillbirth, hypoglycaemia, higher birthweight

diabetes forms), and gestational diabetes mellitus (GDM) (Table I) [2–8].

T1DM is caused by the autoimmune destruction of the insulin-producing beta cells in the pancreatic islets and can be characterised by the appearance of various autoantibodies, including islet cell-, glutamic acid decarboxylase-, insulin-, zinc transporter 8-, and islet antigen-2 autoantibodies. T1DM accounts for the majority of young-onset diabetes cases and shows family aggregation, indicating a genetic background. Result from the study of the Type 1 Diabetes Genetics Consortium showed that human leukocyte antigen (HLA) genes represent almost 50% of the familial risk for developing T1DM, from which HLA class II DR and DQ alleles are the most specific [9, 10]. Recent results suggest that some environmental factors (for example maternal factors, viral infections, and toxic substances) in genetically predisposed subjects may also play a role in the development of T1DM [9]. The immune-mediated pathogenesis in T1DM features islet-specific autoantigens, antigen-specific beta cell-destroying T-cell clones, and the subsequent inflammation of islets. Diabetogenic T-cell clones have been identified both in humans and non-obese diabetic (NOD) mice, the prevailing animal model of T1DM. The early presence of islet autoantigens and diabetogenic T-cell clones prognoses the destruction of the pancreatic beta cells [4, 11–13]. It was thought for a long time that helper CD4<sup>+</sup> T cells mediate the autoimmune destruction of the pancreatic islets through an interaction with Major Histocompatibility Complex (MHC) class II and

T cell receptors, but the impact of cytotoxic CD8<sup>+</sup> T-cell clones through MHC class I was later confirmed too [14].

While T1DM has an autoimmune pathomechanism, T2DM is caused by insulin resistance leading to elevated insulin and glucose levels in blood, but a subsequent beta cell dysfunction may develop at a later time. Genetic, epigenetic, and lifestyle factors — such as obesity, lack of physical activity, incorrect quantity and quality of food — contribute to the development of T2DM. The genetic predisposition of T2DM is confirmed by both heritability estimates and twin studies, genome-wide association studies provided a large number of variants that are associated with a higher risk of developing T2DM, and several candidate genes were identified which have been proven to have a relationship to the disease [15]. T2DM is often developed from metabolic syndrome, which is a complex disease including obesity, dyslipidaemia, insulin resistance, and hypertension [16, 17]. The clinical relevance of T2DM is due to its high prevalence and the associated cardiovascular and other complications (such as nephropathy, neuropathy, retinopathy) that can affect patients' quality of life [5, 18, 19].

GDM is caused by insulin resistance due to the hormonal changes of the placenta in pregnant women, and is characterised by elevated blood glucose and slightly increased insulin levels. Environmental factors such as obesity and genetic factors, for example a first-degree relative who has T2DM, are responsible for its development. GDM endangers both mother and foetus;

**Table II.** The available detection methods for chromogranin A. In routine neuroendocrine tumour diagnostics, the most frequently used techniques for detecting chromogranin A from blood samples are RIA and ELISA [25]

**Tabela II.** Dostępne metody wykrywania chromograniny A. Najczęściej używane techniki detekcji chromograniny A ze krwi w diagnostyce rutynowej guzów neuroendokrynnych to RIA i ELISA [25]

Technique	Type of samples	Comment
Radioimmunoassay <sup>1,2</sup> (RIA) and immunoradiometric assay <sup>1,2</sup> (IRMA) [134, 135]	Serum Plasma	Plasma concentrations are significantly higher [142, 143]
Enzyme-linked immunosorbent assay <sup>1,2</sup> (ELISA) [137, 144]	Serum Plasma	Used in neuroendocrine tumour diagnostics routinely
Time-Resolved Amplified Cryptate Emission (TRACE) [145, 146]	Serum	Currently for research only
Immunohistochemistry <sup>1,2</sup> [147]	Tissue	Used in neuroendocrine tumour diagnostics
Sodium dodecyl sulphate polyacrylamide gel electrophoresis (SDS-PAGE) and immunoblotting (Western Blot) [136]	Saliva	Currently for research only

<sup>1</sup>It is important to emphasise that, in accordance with international recommendations, for proper detection, two-site monoclonal antibody kits (developed by Cisbio) should be used [25, 134–137]

<sup>2</sup>The usage of antacid medications (e.g. proton pump inhibitors or histamine H<sub>2</sub>-receptor antagonists) increase the serum levels of CgA [138, 139]. Therefore, before measurement it is recommended to suspend these type of treatments, if possible, for at least seven days before the test, to avoid false-positive results [28]. Various diseases, including non-oncological gastrointestinal, cardiovascular, and renal conditions, and several tumour types, may also increase the serum levels [33, 140]

it increases the chance of pre-eclampsia, and it may lead to stillbirth if untreated. In 2017, approximately 14% of pregnancies were affected by GDM; however, the prevalence can vary in different populations [19]. After birth, GDM is usually resolved, but the risk of developing T2DM later in life is significantly increased [3, 19, 20].

Chromogranin A (CgA) is a 439 amino acid (48kDa)-long protein expressed by the endocrine and neuroendocrine cells of diverse organs. Several cleavage proteins are generated from CgA, some of which have well-known biological activity, while the exact function of others is unclear. The main intracellular function of CgA is to sort appropriate proteins into secretory granules, while cleavage products act as extracellular regulator molecules. Both the CgA protein and some of its cleavage proteins — including WE-14, pancreastatin and catestatin — show a relationship to carbohydrate metabolism and have significant involvement in diabetes mellitus [21–26].

CgA can be detected from serum, plasma, saliva, or tissue samples using different techniques (Table II). It is one of the most prominent secretory products of neuroendocrine tumours, and therefore its serum level is an informative marker to confirm the diagnosis and to monitor the effectiveness of the treatment [27–32]. However, recent studies indicate that its usage may be limited due to various factors: 1. non-CgA-producing neuroendocrine tumours, 2. other tumour types may produce CgA as well, 3. benign conditions (such as atrophic gastritis or renal dysfunction), and 4. antacid usage may also increase serum CgA levels [33]. Like the whole CgA molecule, WE-14 can also be detected in blood samples [34].

In this review, the available literature on CgA and its cleavage proteins is discussed, focusing mainly on its biochemistry, distribution, and functions, and its relationships to diabetes and carbohydrate metabolism.

## The discovery of chromogranin A and its diabetes-related cleavage products

Chromogranin A (formerly parathyroid secretory protein 1 or pituitary secretory protein I) is a member of the granin glycoprotein family. It is built from 439 amino acids (48kDa) [21]. The name ‘chromogranin’ originates from 1967 when Blashko et. al. isolated soluble proteins from bovine chromaffin granules [35, 36], and the first identified protein was named “chromogranin A” [37].

Nearly half of the hormone peptides of mammals have an amide structure at their C-terminal end for biological activity. To identify peptides containing this alpha-amide structure, an enzymatic release method, which includes thin layer chromatography, was developed. With this method, a large variety of peptides — often without knowing their exact function — were identified [38]. In 1986, from porcine pancreas, a 49 amino acid-long peptide was isolated that was able to inhibit glucose-stimulated insulin secretion. It was named pancreastatin (PST). After the protein’s exact sequence was available, several publications appeared indicating that PST closely resembles some parts of bovine CgA. The relationship between the two proteins was confirmed in 1988, when the complete DNA sequence of the porcine CgA gene, including the full-length PST sequence, was published [38, 39]. This was the first evidence that hormone-like proteins are formed from CgA [38, 40].

WE-14 (the abbreviation comes from N- and C-terminal amino acids and the length of the molecule) was isolated first from human metastatic hepatic cells originating from an ileal carcinoid tumour in 1992 [41], and also proved to be a CgA cleavage product. The peptide was later isolated from human, bovine, and NOD mouse pancreatic beta cells, flask-shaped endocrine cells of intestinal crypts, and porcine adrenal chromaffin cells [11, 42, 43].

In the late 1980s, it was reported that CgA has a cleavage product that can inhibit the nicotine-stimulated catecholamine secretion from cultured adrenal medullary chromaffin cells, but all attempts to identify the active peptide failed until 1997 [44]. The cleaved CgA sections could inhibit significantly more catecholamines than the high molecular weight CgA. To identify the responsible domain within CgA, synthetic CgA-fragments were used to identify the exact cleavage site. The final 20 amino acid-long CgA-fragment was named, after its function, as catestatin (CST). In vivo detection was reported a few years later [45].

### Biological properties of chromogranin A

The human CgA gene (*CHGA*) spans 12 kilobases at q32.12 locus of chromosome 14 and contains eight exons [46–48]. The genes of vertebrate CgA and chromogranin B (CgB), a related member of the granin protein family, belong to two related monophyletic groups, which probably diverged from each other before ancestral fish. In all vertebrate species, CgA contains a large number of glutamic acid, aspartic acid, and hydrophilic proline residues (21%, 4% and 10% in humans), resulting in its acidic and hydrophilic properties [21, 49]. Several regions of CgA, being relatively conserved, exhibit similarities to the calcium-binding domains of well-known calcium-binding proteins such as calmodulin or the vitamin D-dependent calcium-binding protein [50–52]. Two cysteine residues at the N-terminus, which together form a disulphide loop after posttranslational modification, are a common structural characteristic of CgA and CgB in mammals [21, 53–56]. The WE-14 sequence is conserved during evolution, whereas PST and CST have no conserved homologous sequence in non-mammalian CgA proteins, indicating an ancient function of the former, and novel functions related to the latter [57]. These evolutionary patterns of different structural elements of CgA indicate that the intracellular sorting function related to acidic, hydrophilic, and calcium-binding abilities is more ancestral than the majority of the extracellular function related to cleavage products.

Foetal CgA production begins in humans between the 6<sup>th</sup> and 8<sup>th</sup> week of pregnancy in the chromaffin progenitor cells of the adrenal primordia and the

gastrointestinal endocrine cells in stomach, proximal small intestine, distal colon, and rectum [58–61]. In adults, CgA is most abundantly produced by the chromaffin cells of adrenal medulla and the intrinsic neurons of enteric nervous system in the gastrointestinal tract. The presence of CgA can also be detected in the gastrin-producing, the enterochromaffin, and the enterochromaffin-like cells of the stomach, and the glucagon-producing alpha and insulin-producing beta cells of pancreatic islets. CgA-producing neurons reside in the central and other part of peripheral nervous systems such as the postganglionic neurons of the autonomic nervous system, the thyroid-stimulating, luteinising, follicle-stimulating, and growth hormone-producing endocrine cells of the anterior pituitary gland. The calcitonin-producing C-cells of the parathyroid glands also expressed CgA. Moreover, the neuroendocrine cells in lungs, spleen, prostate and thymus, atrial and ventricular cardiomyocytes, wound keratinocytes, the serous cells and ductal cells of salivary glands, germinal epithelial cells, and polymorphonuclear neutrophils also have CgA expression [23, 24, 49, 62–66].

Many extracellular signalling molecules can influence the expression of CgA. Both secretin and gastrin induce CgA transcription [67, 68], while oestradiol inhibits it in the pituitary gland [69, 70], and somatostatin diminishes the circadian rhythm of CgA in blood [71]. The receptors of gastrin and secretin are mainly expressed in the areas of the gastrointestinal tract and pancreas, but chromaffin cells are also responsive to secretin. Signal transduction pathways of protein kinases and extracellular signal-regulated kinases mediate gastrin and secretin extracellular signals via the cAMP response element in the CgA promoter [67, 68, 72, 73].

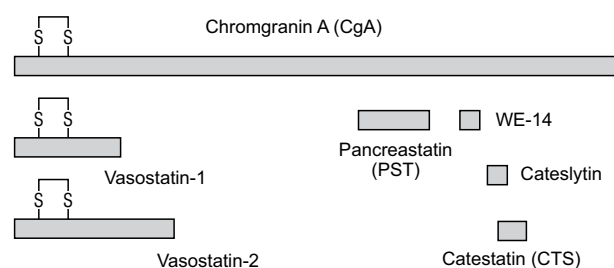
The CgA protein itself is synthesised in the rough endoplasmic reticulum and then transported to the Golgi apparatus. Inside the trans-Golgi network, CgA accumulates in the newly emerging secretory granules [74]. CgA has a high-capacity and low-affinity calcium binding function, which is primarily regulated by the more acidic pH levels inside the maturing secretory granules. The increasing H<sup>+</sup>- and Ca<sup>2+</sup> ion concentrations inside the granules can lead to conformational changes in the protein [75, 76]. Ca<sup>2+</sup> can also enhance the capability of CgA to adhere to membrane [77]. Due to its calcium binding characteristics, after the binding of certain peptide hormones and neurotransmitters, CgA is able to selectively sort and pack these peptides into secretory granules [51, 78]. In Golgi cisterns pH is normally neutral, but the influx of H<sup>+</sup> ions leads to an acidic pH; therefore, the acidic pH-shift induces the aggregation of CgA and its bound peptides into secretory granules. Following the aggregation, the proteins are

locked inside the secretory granules when it detaches from the Golgi apparatus. Non-CgA-bounded peptides and proteins are not included in these granules [54, 75, 79–81].

In parallel with protein and peptide sorting, the posttranslational modification of CgA include glycosylation [82], phosphorylation [83], sulphation [84], carboxymethylation [85], pyroglutamylation [86], the formation of disulphide bonds, two-step proteolytic processing [87–89], and alpha-amidation [38, 90, 91], occurs intracellularly in trans-Golgi network and secretory granules. Biologically active peptides with diverse functions are generated from CgA protein by the cleavage and the subsequent alpha-amidation (Figure 1, Table III). The in vivo isolated cleavage products of CgA in humans include vasostatin-1 and -2, PST, WE-14, cateslytin, and CST [25, 26, 81].

Proprotein convertases 1/3 and 2 (PC1/3 and PC2) are considered as the main enzymes performing the first step of proteolytic processing before secretion [87]. They are intracellular, Ca-activated serine endoproteases with acidic pH optima, and are ubiquitously expressed in endocrine and neuroendocrine cells, features that are logically suited to their localisation and function [92]. Besides CgA, other proproteins such as proinsulin, proglucagon, and proopiomelanocortin are also processed by PC1/3 and PC2. Cathepsin L1 is a lysosomal cysteine endoprotease that mainly contributes to intracellular protein catabolism, but cathepsin L1 in vivo colocalises with CgA in the secretory granules of primary chromaffin cells, and CgA can be a substrate for cathepsin L1 both in vitro and in cella [88]. During the second step of the proteolytic process, carboxypeptidases E and/or D remove the C-terminal, basic amino acid residues after the proteolytic cleavage by PC1/3 and PC2, whereas Arg/Lys aminopeptidase is required to remove the N-terminal basic amino acid residues after the cleavage by cathepsin L1 [89]. After the proteolytic processing, the alpha-amidation of some CgA cleavage products (required for their full biological activity) is catalysed by peptidylglycine alpha-amidating monooxygenase, which is also localised in the trans-Golgi network and secretory granules of endocrine and neuroendocrine cells [93].

About 50% of CgA molecules are proteolytically processed in chromaffin cells before secretion [94], and the further extracellular cleavage of CgA may occur. Chromaffin cells express the components of the serine endoprotease plasmin system: thus plasmin is present in the local environment of the chromaffin cells, and extracellularly cleaves CgA to generate a bioactive product overlapping with CST [95, 96]. Furthermore, plasmin and the serine endoprotease thrombin can also cleave CgA in the bloodstream, in addition to



**Figure 1.** Proportionally scaled chromogranin A protein and its cleavage products isolated from human tissues. A disulphide bridge is located at the N-terminal (left) end of the protein. The exact size of cleavage products: vasostatin-1 — CgA<sub>1-76</sub>; vasostatin-2 — CgA<sub>1-115</sub>; pancreastatin (PST) — CgA<sub>250-301</sub>; WE-14 — CgA<sub>324-337</sub>; cateslytin — CgA<sub>344-358</sub>; catestatin (CTS) — CgA<sub>352-372</sub>

**Rycina 1.** Proporcjonalnie skalowana proteina chromogranina A oraz produkty rozpadu izolowane z tkanek ludzkich. Mostek dwusiarczkowy znajduje się na N-końcowej (lewej) części białka. Dokładna wielkość produktów rozpadu: wazostatyna-1 — CgA<sub>1-76</sub>; wazostatyna-2 — CgA<sub>1-115</sub>; pankreastatyna (PST) — CgA<sub>250-301</sub>; WE-14 — CgA<sub>324-337</sub>; cateslytyn — CgA<sub>344-358</sub>; katestatyna (CST) — CgA<sub>352-372</sub>

their functions in blood coagulation pathway [97] (Figure 2).

Tissue- and cell-specific distribution of CgA cleavage products has been observed [98–100]. However, there is no information on the underlying differences in intra- and extracellular proteolytic processing. For instance, alpha and beta cells of pancreatic islets have a broad immunoreactivity to CgA region-specific antibodies, whereas somatostatin-producing delta and pancreatic polypeptide cells show a limited immunoreactivity [99].

## The role of chromogranin A in type 1 diabetes mellitus

Compared to wild type NOD mice, CgA-deficient knockout NOD mice (NOD.ChgA<sup>-/-</sup>) do not develop T1DM, or this is observed only in a very small portion of the population, suggesting CgA is a causative factor of T1DM; during the 12-month observation period T1DM appeared in more than 90% of the female wild-type NOD mice, while only 3% of NOD.ChgA<sup>-/-</sup> female mice showed any symptoms of the disease. Male NOD.ChgA<sup>-/-</sup> mice had no signs of T1DM at all. Following the 12-month observation period, pathological examinations for insulinitis, the inflammation of the pancreatic islets, was performed. Only 20% of the NOD.ChgA<sup>-/-</sup> mice had developed insulinitis, while insulinitis was present in all the wild-type NOD mice in both genders, and significantly lower amounts of CD4<sup>+</sup> and CD8<sup>+</sup> T-cells were found in the pancreatic tissues of NOD.ChgA<sup>-/-</sup> mice [101].

Table III. Functions of the different chromogranin A (CgA) fragments

Tabela III. Funkcje różnych fragmentów chromograniny A (CgA)

CgA fragment	Species from which it was isolated	Name of the fragment	Function of the fragment	Relation to the carbohydrate metabolism			
				T1DM	T2DM	GDM	Indirect connection
CgA <sub>1-76</sub>	Human	Vasostatin 1	Anti-inflammatory effect [148, 149]				
CgA <sub>1-115</sub>	Human	Vasostatin 2	Antimicrobial effects [150] Cardioprotective and anti-adrenergic effects [151] Vascular permeability inhibition and Endothelial cell proliferation of the blood vessels [152]				
CgA <sub>1-128</sub>	Rat Bovine	β-granin	Inhibition of the parathyroid cell secretion in vitro [153]				
CgA <sub>10-19</sub>	Human	—	Diabetogenic CD8 <sup>+</sup> T-cell autoimmunity [102]	X			
CgA <sub>43-52</sub>	Murine	—		X			
CgA <sub>47-66</sub>	— <sup>1</sup>	Chromofungin	Potent antimicrobial effect through the activation of the polymorphonuclear neutrophils [154, 155]				
CgA <sub>79-113</sub>	Bovine	Vasoconstriction-inhibiting factor (VIF)	Modulation of the vasoconstrictive effects of angiotensin II [156] Counter-regulatory effect against hypertension [156]				
CgA <sub>124-143</sub>	— <sup>1</sup>	Chromostatin	Inhibition of the secretion of chromaffin cells [157]				
CgA <sub>173-194</sub>	Bovine	Chromacin	Inhibition of both Gram-negative and Gram-positive bacteria [158]				
CgA <sub>250-301</sub>	Human Murine Porcine	Pancreastatin	Inhibition of the glucose-stimulated and unstimulated insulin secretion [38, 39, 114, 119, 122] Reduced hepatic glucose uptake [118, 120] Decreased lipid synthesis and leptin secretion in adipocytes [117, 121] Suppressed insulin signalling [114, 132, 159, 160] Metabolic connection to dysglycaemia [161] Higher serum levels in T2DM, GDM, obese hyperinsulinaemic, and obese glucose-intolerant hypertension patients [126, 128, 129]	X	X	X	
CgA <sub>324-337</sub>	Human Murine	WE-14	Diabetogenic CD4 <sup>+</sup> T-cell autoimmunity [11, 104–106]	X			
CgA <sub>344-358</sub>	Human Bovine	Cateslytin	Antibacterial activity: resistance against <i>Staphylococcus aureus</i> , [162], permeabilization of <i>Escherichia coli</i> 's cell wall [163] A novel component of innate immunity [164]				

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## The role of chromogranin A cleavage products in type 1 diabetes mellitus

Some of the newly-discovered autoantigens of T1DM are the cleavage products of CgA: WE-14 is known for its CD4<sup>+</sup> T-cell autoreactivity [11], while other small, N-terminal CgA-fragments have CD8<sup>+</sup>-cell autoimmunity [102].

CgA antigen-specific T cells are selected during the development of the thymus. CgA-specific mRNA is not detectable in embryonal medullary thymic epithelial cells, and this CgA-mRNA deficit may be the cause for

the insufficient amount of CgA-reactive T-cell deletion because there is not enough CgA and/or WE-14 inside the thymus to mediate the deletion [11, 103]. When analysing the structure of the CD4<sup>+</sup> autoreactive WE-14, it was found that despite its common antigen-binding motif, WE-14 is missing the N-terminal amino acids that usually bind easily to the NOD-mouse-specific MHC class II I-A<sup>g7</sup> p1 and p4 antigen-binding sites. These are usually necessary for a stable MHC class II binding. It can be assumed that the C-terminus of WE-14 can interact with the MHC class II I-A<sup>g7</sup> at a site outside of the normal peptide binding groove [11]. Outside

Table III (cont.). Functions of the different chromogranin A (CgA) fragments

Tabela III (cd.). Funkcje różnych fragmentów chromograniny A (CgA)

CgA fragment	Species from which it was isolated	Name of the fragment	Function of the fragment	Relation to the carbohydrate metabolism			
				T1DM	T2DM	GDM	Indirect connection
CgA <sub>352-372</sub>	Human Murine Bovine	Catestatin	Decreased plasma concentration in essential hypertension [165] Counter-regulation of the $\beta$ -adrenergic and endothelin-1 stimulated action [166] and antiadrenergic effect [167] Normalisation of baroreflex [132] Improved insulin sensitivity in catestatin-knockout mice [133] Induction of angiogenesis [168] Antimicrobial activity against bacteria, fungi, and yeasts [164] Antioxidant activity [169] Effective catecholamine release inhibition and endogenous nicotinic cholinergic antagonistic effect [113, 132] Obesity-reducing effects [131]				X
CgA <sub>357-428</sub>	Porcine	Parastatin	Inhibition of the low $\text{Ca}^{2+}$ -stimulated parathyroid secretion in vitro [170, 171]				
CgA <sub>367-391</sub>	Bovine	GE-25	No known biological effect so far [172, 173]				
CgA <sub>417-442</sub>	Murine Rat	Serpinin	A novel, $\beta$ -adrenergic-like cardiac modulator [174, 175]				

<sup>1</sup>Synthetic peptides

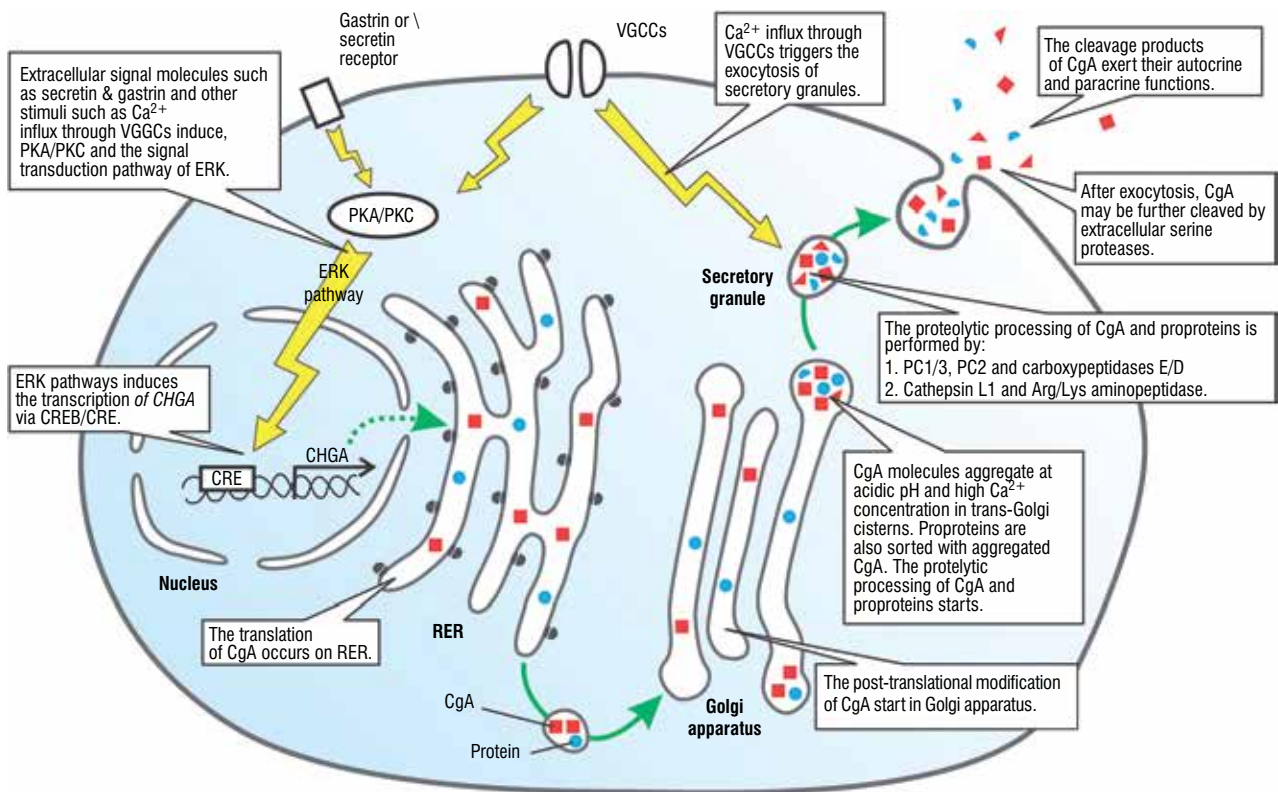
of pancreatic  $\beta$ -cells in NOD mice, the CgA-induced CD4<sup>+</sup> autoimmune reactions of other gastro-entero-pancreatic tissues were not supported [42]. The observation that the CgA-induced autoimmune reaction is only detectable in the beta cells is still unclear to our present knowledge, although several theories have been proposed [11]: 1. Selective autoimmune reactivity is caused by a difference in the proteolytic processing of CgA between beta cells and other cell types of pancreatic islets, or between islet cells and other cells with CgA expression; 2. WE-14 can only function as a pancreatic autoantigen after pancreas-specific post-translational modifications differing proteolytic processing [11].

The antigenic activity of WE-14 can be dramatically increased when modified by enzyme tissue transglutaminase (TGase) [104, 105] or with N-terminal amino acid additions [106]. TGase catalyses the glutamine deamidation of various proteins, changing glutamine to glutamic acid, and covalently crosslinking between the side chains of glutamine and lysine [107]. TGase converts WE-14 from a weak antigen into a potent one for CgA-reactive- and I-A<sup>g7</sup>-restricted-CD4<sup>+</sup> T cells [104]. The higher antigenicity of WE-14 is caused by the crosslinking, while the antigenic strength of deamidated WE-14 is similar to the unmodified molecule [34]. While healthy controls appear normal, newly diagnosed T1DM

patients have shown elevated WE-14 antigenicity in their blood samples, which can be increased by in vitro TGase treatment. How often these modifications of WE-14 by TGase can occur in the pancreatic beta cells in vivo is currently unknown, but it was suggested that the increased immune response may develop due to aberrant post-translational modifications [105].

Different NOD mouse T-hybridoma cell lines carrying different structural variants of T-cell receptors are responsive to low concentrations of a WE-14 that has been modified with an N-terminal arginine-leucine-glycine-leucine addition (RLGL-WE14) in vitro. Reverse proteolysis or transpeptidation mechanisms may play a major role in the generation of RLGL-WE-14, which occur after the cleavage product is cleaved by the proprotein convertases from the original CgA molecule [106].

Human association studies [108–110] and a subsequent animal study with humanised NOD mice verified that the presence of human HLA-A\*0201 serotype is an important contributor to the development of T1DM [110]. Samples from HLA-A\*0201-positive transgenic NOD mice and onset HLA-A\*0201-positive T1DM patients diagnosed within one year showed CgA-fragment-related CD8<sup>+</sup> T-cell autoimmunity [102]. Human CgA<sub>10-19</sub><sup>1</sup>, CgA<sub>43-52</sub> and murine mCgA<sub>10-19</sub> and mCgA<sub>43-52</sub> fragments that have been exposed to splenic CD8<sup>+</sup> T-cell clones displayed



**Figure 2.** The gene expression, post-translational modification, secretion, and functions of chromogranin A. CgA — chromogranin A; CHGA — CgA gene; CRE — cAMP response element; CREB — cAMP response element-binding protein; ERK — extracellular signal-regulated kinase; PC1/3 and PC2 — proprotein convertases 1/3 and 2; PKA/PKC — protein kinase A and C; RER — rough endoplasmic reticulum; VGCCs — voltage-gated Ca<sup>2+</sup> channels

**Rycina 2.** Ekspresja genu, modyfikacja potranslacyjna, wydzielanie i funkcje chromograniny A. CgA — chromogranina A; CHGA — gen CgA; CRE (cAMP response element) — element odpowiedzi na cAMP; CREB (cAMP response element-binding protein) — białko wiążące element odpowiedzi na cAMP; ERK (extracellular signal-regulated kinase) — kinaza regulowana zewnątrzkomórkowo; PC1/3 and PC2 (proprotein convertases 1/3 and 2) — konwertazy proproteinowe 1/3 i 2; PKA/PKC (protein kinase A and C) — kinaza A i C; RER (rough endoplasmic reticulum) — retikulum endoplazmatyczne szorstkie; VGCCs (voltage-gated Ca<sup>2+</sup> channels) — kanały wapniowe potencjałozależne

induced T-cell proliferation and increased cytotoxic activity. The same could not be observed in healthy controls nor in HLA-A\*0201-negative T1DM patients.

## Chromogranin A in type 2 diabetes mellitus

Both the salivary and serum levels of CgA were significantly higher in T2DM patients than in healthy control subjects, and higher CgA concentrations were more frequently observed in the poorly controlled patients. Furthermore, a significantly higher number of various periodontal diseases occurred in both the well- and poorly-controlled diabetic groups with higher CgA levels [111]. Impaired salivary flow was correlated with significantly higher salivary and serum CgA levels. Two genetic variants of CHGA (rs9658635 and rs9658655) were associated with lower salivary flow and higher salivary CgA concentrations in T2DM [112].

CHGA knockout (CgA-KO) mice are obese on normal chow diet [113], have significantly higher glucose-stimulated insulin secretion after glucose administration [114], have hypertension with higher catecholamine levels [113], and have insulin resistance in muscle cells [115]. Lower triglyceride levels have been found in CgA-KO mice, despite similar amounts of fatty tissue [116].

## The role of pancreastatin in the carbohydrate metabolism, in gestational and type 2 diabetes mellitus

PST is a negative regulator of insulin sensitivity and glucose homeostasis: Hyperglycaemia (a high glucose level in blood) can be at least partly promoted by the PST-mediated inhibition of insulin secretion. In addition, PST also increases blood glucose levels by reducing the hepatic glucose uptake through the inhibition of the insulin-stimulated glycogenesis in primary hepatocytes,



decreasing the insulin-stimulated synthesis of lipids, and regulating the expression and secretion of leptin in adipocytes [38, 39, 117, 118]. In hepatocytes and adipocytes, this is mediated by the G-protein activated phospholipase C  $\beta 3$  isoforms (PLC- $\beta 3$ ). PLC- $\beta 3$  causes a cytosolic increase of intracellular  $\text{Ca}^{2+}$  ion concentration through inositol trisphosphate signalling, and the promotion of phosphokinase C (PKC) and mitogen-activated protein kinase pathways [119–122]. Several studies suggest that the insulin inhibition by PST in hepatocytes is also carried out through the activation of the nitric oxide (NO) pathways. NO has a known inhibitory function on insulin [123], while PST can increase NO production [114, 124].

The euglycemic state of the CgA-KO mice is maintained by the increased liver insulin sensitivity. Euglycaemia can be inhibited by the suppression of phosphoenolpyruvate carboxykinase (PEPC) and glucose-6-phosphatase (G6Pase) mRNAs, which leads to hypoglycaemia. Even in the absence of PEPC and G6Pase mRNAs, euglycaemia emerged with the administration of external PST. In hepatocytes transfected with the G6Pase promoter fused with a luciferase reporter, the external PST induced an approximately six-fold transcriptional activation in a PKC- and NO synthetase-dependent manner, which ultimately suppresses insulin signalling [114].

PST influences the physiological homeostasis of blood glucose and insulin in humans. Fasting PST levels of T2DM patients have no significant difference compared to those of control subjects, but postprandial PST concentrations are significantly higher in T2DM patients during an oral glucose tolerance test (OGTT) [125]. The PST hypersecretion in pancreatic cells of T2DM patients may be due to the inhibition of the glucose-induced insulin secretion, ultimately resulting in hyperglycaemia [126]. PST levels of obese T2DM patients are significantly higher compared to those in non-diabetic obese patients and healthy control subjects. After a two-month supervised weight loss, PST concentrations did not change in these groups [127]. Like in T2DM patients, non-obese, essential hypertension patients with pre-diabetic symptoms (hyperinsulinemia or glucose-intolerance) had significantly increased postprandial PST levels during OGTT [128]. An increase (approximately one and a half-fold) in PST serum level was found in GDM patients, and a positive correlation between different catecholamines (epinephrine, norepinephrine) and PST levels was also observed [129].

### The presumed role of catestatin in carbohydrate metabolism

Concerning diabetes and carbohydrate metabolism, in the case of CST, only indirect correlations are available. Some authors assume that the peptide may contribute

to the development of metabolic syndrome and diabetes mellitus. Its possible use as a future treatment for obesity and hypertension was also considered [130].

The bodyweight of obese CgA-KO mice [113] can be reduced to that of wild-type mice by administering external CST. The obesity-reducing effects are due to inhibition of  $\alpha_2$ -adrenergic receptor signalling and the enhancement of leptin receptor signalling [131].

CgA-KO mice have been shown to have hypertension, diminished baroreflex sensitivity, and increased catecholamine secretion. By external administration of CST, catecholamine levels and baroreceptor functions can be normalised to wild type values [132].

In the pathomechanism of the obesity-induced insulin resistance and the consequential T2DM, the activation of hepatic Kupffer cells and monocyte-derived recruited macrophages have a crucial effect. CgA-KO mice were fed on a high-fat diet to create diet-induced obesity. Mice had elevated insulin and blood glucose levels, compared to wild type mice. External CST treatment normalised the glucose metabolism of hepatocytes and improved the insulin sensitivity of the mice by decreasing various circulating and hepatic lipid fractions, inflammatory cytokines, and via proinflammatory gene expression of hepatic Kupffer cells and macrophages. CST also had direct anti-inflammatory effects, decreasing macrophage activation and recruitment to the liver [133].

### Conclusions

CgA is produced by various endocrine and neuroendocrine cell types of the different organs, where it plays an important role in the intracellular storage and selective secretion of various hormone peptides in the human body. During and after its secretion, it is cleaved, modified, and converted into biologically active extracellular peptide forms. The CgA cleavage products, such as WE-14, pancreastatin, and catestatin, all have significant and specific biological effects.

Recent studies suggest that the cleavage products of CgA contribute to the development of different diabetes mellitus forms. WE-14 fulfils a function as an autoantigen for both the diabetogenic, pancreatic beta cell-destroying  $\text{CD4}^+$  and  $\text{CD8}^+$  T cell populations in humans and in a NOD mouse model. CST and PST have regulator roles in T2DM and GDM.

Based on the impact of the currently available knowledge, and the wide range of functions of CgA-derived peptides, further studies are needed to investigate the possible treatment options and the relationships between diabetes mellitus, CgA, and its cleavage products.

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