frontiers in Clinical Diabetes and Healthcare

TYPE Mini Review
PUBLISHED 13 April 2026
DOI 10.3389/fcdhc.2026.1812936

Check for updates

OPEN ACCESS

EDITED BY
Arrigo Francesco Giuseppe Cicero,
University of Bologna, Italy

REVIEWED BY
Raelene Pickering,
Monash University, Australia

*CORRESPONDENCE
Elke M. Muntjewerff
elke.muntjewerff@mcb.uu.se

RECEIVED 17 February 2026
REVISED 20 March 2026
ACCEPTED 23 March 2026
PUBLISHED 13 April 2026

CITATION
Christoffersson G and Muntjewerff EM (2026) The role of chromogranin A cleavage products in onset of type 1 and 2 diabetes. *Front. Clin. Diabetes Healthc.* 7:1812936. doi: 10.3389/fcdhc.2026.1812936

COPYRIGHT
© 2026 Christoffersson and Muntjewerff. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

The role of chromogranin A cleavage products in onset of type 1 and 2 diabetes

Gustaf Christoffersson [1,2] and Elke M. Muntjewerff [1*]

[1]Department of Medical Cell Biology, Uppsala University, Uppsala, Sweden, [2]Science for Life Laboratory, Uppsala University, Uppsala, Sweden

Chromogranin A (CgA) is a pro-hormone widely expressed in neuroendocrine tissues and elevated in both type 1 (T1D) and type 2 diabetes (T2D). Its diverse biological effects arise from proteolytic cleavage into six bioactive peptides: vasostatin I and II (VS-I/II), chromofungin (CHR), pancreastatin (PST), catestatin (CST), WE-14, and serpinin—each exerting distinct and sometimes opposing functions. This review covers current knowledge on the activity, circulating levels, and mechanistic roles of these peptides in diabetes pathogenesis and progression. Evidence indicates contrasting peptide profiles in T1D and T2D: PST levels are elevated in T2D and promote inflammation, gluconeogenesis, and insulin resistance, whereas CST levels are reduced and exert anti-inflammatory and insulin-sensitizing effects. In T1D, CST and VS-I are increased early after diagnosis, with VS-I and WE-14 functioning as autoantigens that drive autoreactive T cell responses. Knockout mouse models further demonstrate that loss of CgA or CST profoundly alters glucose homeostasis, macrophage polarization, catecholamine release, and diabetes susceptibility. Emerging data highlight a complex nerve–immune–endocrine axis through which CgA peptides regulate metabolic and inflammatory pathways. Collectively, CgA-derived peptides represent promising biomarkers and therapeutic targets, though further translational studies remain essential to define their diagnostic and clinical potential.

KEYWORDS
catestatin, chromogranin A, diabetes type 1, diabetes type 2, pancreastatin, serpinin, vasostatin, WE14

1 Introduction

High levels of the pro-hormone chromogranin A (CgA) are associated to neuroendocrine tumors and many metabolic, cardiovascular, inflammatory and autoimmune diseases (e.g. inflammatory bowel disease, rheumatoid arthritis) (1). High levels are also found in the saliva and blood of individuals with type 2 diabetes (T2D) and type 1 diabetes (T1D) (2–5). CgA is produced and released by neurons and (neuro) endocrine cells, such as enteroendocrine cells in the gut, chromaffin cells in the adrenal medulla and alpha (α) and beta (β) cells in the pancreas (1). It's striking that elevated CgA levels are detected in various disease types despite varying disease mechanisms. This variability is probably due to the fact that CgA is cleaved into bioactive cleavage products based on the factors in the environment (6). CgA can be cleaved in storage vesicles within the cell or extracellularly upon release by various proteases including furin, prohormone

convertases (PC) 1 and 2, cysteine protease cathepsin L (CTSL), the serine proteases plasmin, kallikrein and thrombin (7). Cleavage can result in the six bioactive peptides vasostatin (VS) I or II, chromofungin (CHR), pancreastatin (PST), catestatin (CST), WE-14 and/or serpinin. Since all six bioactive cleavage products have their own specific modes of function, which can even be opposing, this could drive diseases. Although it is clear from literature that CgA plays an important role in regulating different homeostatic processes (1, 7, 8), the knowledge on how its bioactive cleavage products are contributing to diseases like T1D and T2D is currently scattered. In this review, we aim to summarize the current findings of the CgA cleavage product functions and their therapeutic potential in the perspective of diabetes and point out the current knowledge gaps with suggestions on how to move the field forward. Understanding the precise roles and balance of CgA cleavage product levels in diabetes progression would help to understand disease development, advance diagnostics and possible treatments for future patients.

2 Main part

2.1 Chromogranin A polymorphisms in diabetes onset

Sequencing of the *CHGA* gene locus in several human populations shows common and rare genetic variations in the open reading frame and regulatory regions (such as the proximal promotor and 3´UTR) that influence CgA expression and function (9). Variations that may affect function are specifically observed between Asian and White populations, as well as between Iranian and White males and females (9–11). More clinical studies show that the common genetic variations of the *CHGA* gene are associated with hypertension, hypertensive renal disease and T2D (5, 11–13) possibly by effecting sympathetic activity and endothelin (ET-1) secretion (13, 14). These effects are likely the result of affected generation and function of the bioactive CgA cleavage products. In line with this theory, the PST variant Gly297Ser is an identified risk factor for T2D onset in an Indian population (15, 16). However, more research is necessary to determine the exact role of *CHGA* polymorphisms in T1D and T2D onset and to highlight its potential as biomarker.

2.2 Activity and blood levels of CgA derived bioactive peptides in diabetes

CgA and its cleavage products can be detected in plasma, serum or saliva from individuals using ELISA or radioimmunoassay (RIA). So far, studies show quite consistent and stable levels in healthy individuals (0.5–5 nM) (17), but it should be taken into account that medication and diet could affect circulating CgA levels (NCT02620696, NCT00166725, NCT03288402). For CgA, increased levels are detected in saliva and blood of individuals with T2D and T1D (2, 3), where for T1D the CgA blood levels rise early on in T1D onset or when gut related complications arise (4, 18). Since CgA is processed and cleaved differently during inflammation, the blood levels, and perhaps most importantly, the balance between the CgA cleavage products might tell us more about the disease progression (6). Therefore, we summarized the currently known CgA cleavage product blood levels in T1D and T2D onset (Table 1).

2.2.1 Vasostatin levels are low in T2D, but high in T1D

VS-II is seen as an anti-inflammatory peptide since it inhibits monocyte and macrophage recruitment (19). In line with this, plasma VS-II levels are low in individuals with T2D and are associated with poor coronary collateral vessels in diabetic chronic total occlusions patients (20, 21). For autoimmune diabetes, there is limited human data, but in the streptozotocin-induced mouse diabetes model, which mimics T1D by β-cell destruction, VS-II treatment promoted post-ischemia arteriogenesis and angiogenesis following femoral or coronary artery occlusion (20). If VS-II levels would already have been high, this treatment would likely not have had an effect. At the moment its unknown if VS-II levels in mice reflect the VS-II levels in humans with T1D. In contrast, $CgA_{1\text{-}439}$, VS-I ($CgA_{1\text{-}76}$) and serpinin ($CgA_{410\text{-}439}$) inhibit spontaneous and VEGF- or bFGF-induced

TABLE 1 Overview of the chromogranin A (CgA) cleavage products and their presence in type 1 diabetes (T1D) and/or type 2 (T2D) diabetes.

CgA cleavage product	T1D	T2D	Functions related to diabetes	REFS
Vasostatin I $CgA_{1\text{-}76}$	? (↑)	? (↓)	VS-I parts that act as autoantigen in mice: $_{m}ChgA_{10–19}$, $_{m}CgA_{29\text{-}42}$, $_{m}ChgA_{34–42}$ and $_{m}CgA_{36\text{-}44}$, $_{m}ChgA_{43–52}$ VS-I parts that act as autoantigen in human: $_{h}ChgA_{10–19}$ and $_{h}ChgA_{43–52}$ Inhibits angiogenesis and vasoconstriction, anti-adrenergic	(23–27, 61, 62, 64)
Vasostatin II $CgA_{1\text{-}113}$	? (↓)	↓	Promotes angiogenesis, anti-inflammatory	(20, 21) (19)
Chromofungin $CgA_{47\text{-}66}$	? (↓)	? (↓)	Anti-inflammatory, antifungal, cardioprotective	(28–30, 32, 33)
Pancreastatin $CgA_{250\text{-}301}$	(↑)	↑	Pro-inflammatory, pro-gluconeogenic, anti-insulin, pro-glucagon	(34–37)
Catestatin $CgA_{352\text{-}372}$	↑	↓	Anti-inflammatory, antimicrobial, anti-gluconeogenic, pro-insulin, anti-glucagon, anti-adrenergic, pro-angiogenic, affects leukocyte migration	(4, 38–44)
WE-14 $CgA_{324\text{-}337}$	? (↑)	? (↓)	Autoantigen	(23, 49–53)
Serpinin $CgA_{402\text{-}439}$	?	?	Cardiac function, cardioprotective, regulates granule biogenesis, anti-apoptotic, inhibits angiogenesis	(22, 55–60)

high levels ↑, low levels ↓ or unknown with speculation ? (↑)(↓), and their function including the references (REFS).

angiogenesis from HUVECs grown on Matrigel or in the aortic ring model of angiogenesis (22).

For VS-I, levels are increased in mouse autoimmune diabetes models, non-obese diabetic (NOD) mice, and human pancreas treated with inflammatory cytokines (23, 24). Although it remains to be confirmed in human plasma, we may expect that VS-I levels will be increased in individuals with T1D. This may further link to the disease as parts of VS-I (Table 1) act as an autoantigen in T1D, which results in the presence of VS-I-specific $CD4^+$ and $CD8^+$ T cells (23, 25, 26). These T cells are present in the pancreatic draining lymph nodes and islets in NOD mice, where their amounts increase during disease progression (25). The injection of $CgA_{36–44}$ primed $CD8^+$ T cells or $CgA_{29–42}$ naïve splenocytes to mice on a NOD/severe combined immunodefiency (SCID) background results in progression to diabetes (25, 26), which suggests that VS-I drives autoimmune diabetes onset. CgA-specific $CD8^+$ T cells and $CgA_{29–42}$ autoantibodies are detectable in blood from NOD mice and individuals with T1D (23, 27). In this perspective, it might be useful to screen VS-I, autoantibodies to VS-I or CgA-specific $CD8^+$ T cells in the blood of individuals with high risk of developing T1D.

2.2.2 Chromofungin maintains homeostasis, but its role in diabetes is currently unclear

Little is known about CHR in general and currently there is no simple detection method via plasma or saliva available. However, ulcerative colitis (UC) patients display decreased CHR expression in gut biopsies when compared to healthy individuals (28, 29). Moreover, CHR is cardioprotective (30, 31), antifungal (32) and anti-inflammatory (28, 29, 33). CHR supplementation improved cardiac function by negative inotropism without changing coronary pressure on isolated frog and rat hearts, a mechanism which pharmaceuticals for hypertension and chronic heart failure target. Moreover, administration of CHR after a myocardial infarct improves the infarct size and lactate dehydrogenase levels (30, 31). Based on this, CHR seems to play a role in maintaining cardiovascular homeostasis, which would make it an interesting CgA cleavage product to study in the context of diabetes-related cardiovascular complications.

2.2.3 Pancreastatin and catestatin plasma levels and functions are opposite in diabetes

Individuals with T2D and pregnant women with gestational diabetes display higher PST levels than healthy individuals (34) (35, 36). This rise of PST levels correlates with its proposed functions, since it's been shown to decrease glucose uptake (34), which is affected during T2D. PST is pro-inflammatory, pro-gluconeogenic, inhibits insulin function and promotes glucagon function (34–37).

In contrast to PST, CST levels are low in T2D (38). This is in line with the notion that PST and CST have opposite effects in the regulation of pancreatic islet homeostasis and inflammation (further discussed in section 2.3). CST is known to be anti-inflammatory, anti-gluconeogenic, to promote insulin function, to inhibit glucagon function, be antimicrobial, anti-adrenergic, induce cytokine production, pro- angiogenic, and is chemotactic, but blocks leukocyte migration in an inflammatory environment (C-X-C motif chemokine ligand 2 (CXCL2) or CC-chemokine ligand 2 (CCL2) (4, 38–44).

Individuals with T1D display increased plasma CST levels, especially in the first 3 years after diagnosis (4, 43). There is only one study that looked into PST levels in T1D, which reported a slight increase in basal PST levels and a significant rise in PST levels upon glucose ingestion, when compared to healthy individuals (37). It would be interesting to study also how the balance between PST and CST levels changes during T1D progression.

2.2.4 WE-14 triggers an autoantigenic T cell response in T1D but its blood levels are unknown

There is currently no data available on WE-14 plasma levels in diabetes, which is surprising since it is possible to detect WE-14 plasma levels with commercial ELISA kits (45, 46). For example, WE-14 levels are reported to be increased in individuals with pheochromocytoma before treatment and normal after surgical removal of the tumor (46). It would be interesting to measure WE-14 levels in individuals with high risk of T1D or at early disease onset since WE-14 triggers an autoreactive $CD4^+$ T cell response during disease onset in T1D individuals and NOD mice (47, 48). Although WE14 is mostly mentioned for its properties as an autoantigen in T1D, it seems like VS-I (also an autoantigen) footpad injections to NOD mice induces stronger T cell proliferation in the draining popliteal lymph nodes than WE-14 (23, 49). It can simply be due to the fact that WE-14 was discovered earlier than VS-I, as a result of improved detection methods, or that WE-14 might indeed trigger a stronger autogenic response than VS-I by forming a hybrid-insulin peptide (HIP) or post-translational modifications inducing a stronger response then wildtype WE-14 only (49–53). Regardless of the immunogenicity, measuring WE-14 blood levels or HIP-reactive T cells during T1D onset could serve as a biomarker (54). Based on this knowledge, we would expect WE-14 levels to be high in T1D and low in T2D.

2.2.5 Serpinin affects heart function and granule biogenesis, but its role in diabetes is unknown

At the moment we know very little about serpinin, this might be due to its subsequent processing into various serpinin peptides including full serpinin, pGlu-serpinin and serpinin-RRG. The serpinins seem involved in heart function (myocardial contractility), inhibits angiogenesis, regulate granule biogenesis in (neuro) endocrine cells and have an anti-apoptotic effect on neurons and endocrine cell lines (22, 55–60). To exert its effect on the heart the pGlu-serpinin and full serpinin require the β1-adrenergic receptor (56), which is opposite of CST and VS-I which seem to induce anti-adrenergic cardioinhibitory effects (44, 61, 62). This interplay of CST, VS-I and serpinin on cardiac function should be investigated in the same model to understand the balance of their functions in homeostasis and therapeutical potential for individuals with diabetes. There is currently no data on serpinin plasma levels available, but serpinin has been detected in endocrine cells and organs (heart, nerve fibers in the skin, eye, dental pulp) via immunoreactivity assays, customized

ELISAs and a commercially available ELISA kits (56–58, 63). Thus, more research is necessary to understand the function of serpinins and their therapeutical potential.

Altogether, the contrasting CgA cleavage product levels in T1D and T2D onset already show that they likely play a crucial role in disease onset (Figure 1). In the future, the profile of CgA cleavage products in plasma could function as a biomarker to predict diabetes onset and/or follow disease progression.

2.3 Diabetes onset is affected by the absence of CgA or CST

The absence of CgA in mice results in major phenotypic changes including increased heart rate, hypertension and heart morphology (increased left ventricular mass and cavity dimensions), increased abdominal fat in the first 6 months of age and elevated plasma adipokines, isoprostane, reactive oxygen species (ROS), neuropeptide Y, plasma and adrenal catecholamines, and adrenal ATP content (65–69). Additionally, CgA-KO mice have smaller islets, altered islet endocrine cell composition, and a lower islet density when compared to WT mice (43, 66). CgA-KO mice also display enhanced insulin sensitivity when maintained on a normal chow diet (NCD) (70, 71), which persisted even after four months of high-fat diet (HFD) (72). Moreover, diet-induced obesity (DIO) via HFD on CgA-KO mice resulted in decreased hepatic gluconeogenic and proinflammatory as well as an increase in anti-inflammatory genes in white adipose tissue and peritoneal macrophages when compared to wildtype (WT) DIO mice (72). Strikingly, crossing the CgA-KO mice with the NOD mouse model does no longer result in the development of T1D (73, 74). In contrast to normal NOD mice, the CgA-KO NOD mice show no signs of insulitis in the pancreas, but they do display lymphocytic infiltrate in the salivary glands similar as to NOD mice (73). CgA-reactive T cells still develop in the absence of CgA similarly as in NOD mice, but the difference is that in the CgA-KO mice the T cells remain naïve (73). This might be due to the lack of the autoantigens WE-14 and VS (23–27, 49–53), and the formation of hybrid-insulin peptides. The question arises what the contribution is of the other CgA cleavage products in the development of T1D and T2D.

Although CgA has six cleavage products, only a knockout mouse for CST has been generated to our knowledge (75, 76). Mice lacking CST show low grade organ inflammation, increased plasma catecholamines, chemokines (CXC-1, CCL-2) and inflammatory cytokines (IL-6, TNF-α, IL-1β), increased anti-inflammatory cytokine IL-10, an impaired epithelial barrier, and less gut microbiota diversity (43, 75–77). From the perspective of diabetes, CST-KO mice are very interesting since they are obese, eat more food, display hypertension and are insulin resistant (75, 76) (43). Moreover, pancreatic islet morphology and composition is affected, where like CgA-KO mice, also CST-KO mice have fewer endocrine cells per islet and a decrease in number of β cells (43).

To learn more about the role of CgA cleavage products in diabetes, researchers use CgA-KO, CST-KO and models for T1D (NOD) or T2D (ob/ob, DIO) either with or without CgA cleavage product, CST/PST/VS-I/VS-II/CHR/serpinin, supplementation.

2.4 PST and CST oppositely control endocrine function and insulin sensitivity

In vivo glucose tolerance tests (GTT) and pyruvate tolerance tests (PTT) in mice lacking CgA or CST shows affected glucose homeostasis, where deletion of CgA results in increased insulin sensitivity, but deletion of only the CST domain results in decreased insulin sensitivity (43). But which CgA cleavage product is responsible for the increased insulin sensitivity?

Healthy individuals show a decrease in forearm *in vivo* glucose uptake following 20 minute PST supplementation via brachial arterial infusion, but not for CST supplementation (34). Moreover, PST supplementation to CgA-KO mice reverses their insulin sensitivity and inflammatory factors, but does not affect the weight gain when compared to WT DIO mice (72). In line with this, supplementation of PSTv1 (PST-NΔ3: $CHGA_{276–301}$), which lacks PST activity, to WT-DIO mice improved insulin sensitivity and glucose tolerance (72). To confirm if the opposite effects on glucogenesis indeed originate from PST and CST presence, CgA-KO mice where supplemented with PST and/or CST for 4 weeks followed by pyruvate tolerance tests (PTT), which indeed showed increased glucose levels upon PST and decreased glucose levels upon CST supplementation (43). Thus, PST and CST have opposing effects in gluconeogenesis, where PST promotes and CST suppresses gluconeogenesis.

The lack of CST also results in lower basal insulin, C-peptide and glucagon levels, which normalize upon CST supplementation (43, 76). In line with this, glucose stimulation of CST-KO mice does no longer result in a rise in insulin plasma levels when compared to WT and CgA-KO mice (43). Also, suppression of glucagon secretion after glucose stimulation was no longer observed in mice lacking CgA or CST when compared to WT mice (43). These findings are in line with the increased insulin sensitivity in CgA-KO and insulin resistance as observed in CST-KO mice (70, 71, 76). Interestingly, islets lacking CST can produce insulin since *in vitro* high glucose stimulation of pancreatic islets isolated from CST-KO mice does result in major insulin release when compared to WT and CgA-KO mice (43). This discrepancy between *in vitro* and *in vivo* is probably due to the presence of catecholamines *in vivo*, which can inhibit insulin secretion via α_2-adrenergic receptors on beta cells (78, 79). However, this theory should be tested in the future. The role of catecholamines in the onset of diabetes is discussed in more detail in section 2.4.

Since insulin injection in WT mice results in reduced PST plasma levels when compared to basal levels (68), it is likely that also here PST and CST have opposing effects. Indeed PST supplementation to CgA-KO mice inhibits insulin secretion upon glucose stimulation, while CST supplementation results in normal increased insulin plasma levels (43). Moreover, CST supplementation to DIO mice shows decreased plasma insulin levels, lower expression of gluconeogenic genes (*G6pc* and *Pck1)* and improved insulin sensitivity (76). Normal DIO and CST-KO

DIO mice display increased plasma insulin levels after 8 hours of fasting, where supplementation of CST brings the plasma insulin levels down for both mice (76), again showing the importance of CST in controlling insulin sensitivity. These findings may be promising for potential exploitation in treatments for T2D since these patients also display low CST plasma levels that correlate with body weight, insulin, glucose and lipid levels (38).

In summary, PST and CST have opposite effects in islet endocrine function and thereby both play a crucial role in maintaining islet homeostasis. In T1D and T2D the function of the islet is disturbed, in the future the supplementation of CST or PST might be an interesting therapeutic (as discussed in section 2.5) to control gluconeogenesis, insulin and glucagon levels, especially in T2D (Figure 1).

2.5 CgA cleavage products affect macrophages which interfere in diabetes progression

2.5.1 PST has inflammatory, while VS-II, CST, CHR have anti-inflammatory effects via macrophage polarization and migration

DIO mice are characterized with an inflammatory macrophage profile, but upon CgA depletion the CgA-KO DIO mice display a more anti-inflammatory profile. PST seems to enhance this inflammation since PST supplementation to CgA-KO DIO mice shows an inflammatory profile similar to normal DIO mice (72). Moreover, PST treatment of WT or CgA-KO peritoneal macrophages shows an increase in inflammatory marker expression (*Nos2, Tnfα, Mcp1, Il6*) (72). In contrast, upon CST supplementation, normal DIO mice show reduced monocyte-derived macrophage ($F4/80^{-}Ly6C^{+}$) infiltration in the liver (76). CST and PST are known to be chemotactic for leukocytes (42, 72). However, *in vivo* and *in vitro* migration assays show that if CST is present in an inflammatory environment, it blocks migration towards inflammatory chemokines (CCL2, CXCL2) (42), which would explain the observed reduced liver infiltration in DIO mice. Additionally, liver macrophages isolated from DIO mice supplemented with CST *in vivo* or *in vitro* showed a reduction of pro-inflammatory genes (*Emr1, Itgam, Tnfa, Ifng, Nos2, Ccl2*) and an increased expression of anti-inflammatory genes (*Il-10, Clec10a*) when compared to liver macrophages from normal DIO mice (76). Not only CST, but also VS-II and CHR have shown beneficial effects on leukocyte migration and polarization in inflammatory diseases.

Administration of VS-II to atherosclerotic (apolipoprotein E-deficient ($ApoE^{-/-}$)) mice on high-fat diet showed reduced expression of inflammatory and chemoattractant markers (TNF-α, MCP-1, VCAM-1) in aortic tissues (19). Additionally, *in vivo* and *in vitro* migration assays confirmed that VS-II treatment suppresses leukocyte adhesion to the vessel wall and monocyte and macrophage migration (19). For CHR, its intra-rectal (*i.r.*) administration to dextran sulfate sodium (DSS) induced colitis mice has a beneficial effect on colitis progression, which also seems related to the effect on macrophages, monocytes and neutrophils. CHR administration to DSS mice or LPS-treated macrophages *in vitro* resulted in reduced (myeloperoxidase) MPO, C-reactive protein (CRP), monocyte chemoattractant protein-1 (MCP1) protein, NF-κBp65 protein levels, reduced mRNA expression of inflammatory markers (*Tnfα, Il1b, Il6, Tlr4 and Rel*) and macrophage inflammatory factor (*mip1a* and *mip1b*) when compared to PBS or scrambled CHR peptide (sCHR) treatment (29). *In vivo* or *in vitro* CHR-treated peritoneal macrophages of DSS-colitis WT mice show a more anti-inflammatory profile since they express higher levels of *Il10*, arginase-1 (*Arg1*), chitinase-like protein (*Ym1*) and found in inflammatory zone protein (*Fizz1*) (28). Although not tested in a diabetes model, the beneficial effects of CHR and CST on macrophage polarization and migration seem similar. The question arises if they would compete or collide with each other when supplemented at the same time. CHR and CST can both induce a concentration-dependent transient increase of intracellular calcium *in vitro* in human polymorphonuclear neutrophils (PMNs) (33). Addition of both peptides at the same time showed a higher calcium increase than separate peptide stimulation. This suggests that CHR and CST enhance each other's functions rather than opposing each other (33). More research is necessary to define the exact effect of CHR on the function of neutrophils, monocytes and macrophages. Additionally, it would be very interesting to investigate if this increase in positive effect on inflammation is also observed upon VS-II, CHR and CST treatments in diabetes models.

2.5.2 CST exerts its beneficial effects in diabetes progression via macrophages

Macrophages are known to play a key role in the development of T1D since clodronate treatment of autoimmune diabetic mice (RIP-LCMV-GP and NOD) resulted in reduced T1D onset (80). Strikingly, depletion of macrophages via clodronate treatment in DIO mice supplemented with CST no longer results in improved glucose tolerance and insulin sensitivity (76). Thus, it seems like the macrophages (or other phagocytes that are affected by clodronate treatment) are key players in exerting the beneficial effect of CST in diabetes onset. Some researchers claim that CST can even be produced by macrophages (75), while others show the opposite (6). Nevertheless, it would be possible for the macrophages to receive vesicles containing either CgA or its cleavage products from neurons or (neuro)endocrine cells that can be released in the liver or pancreas to interfere locally (81). Although not tested for diabetes, it is plausible that CST exerts its beneficial effect in diabetes progression via macrophages.

2.5.3 CST interferes in nerve-immune-endocrine communication via catecholamines

Increasing amounts of data from both human histopathological and mouse studies point to an active involvement of neuronal input to the immune environment in T1D onset. Human T1D pancreata show signs of sympathetic neuron loss at early disease onset (82), and even in pre-symptomatic autoantibody-positive individuals (83). In mouse models, interfering with pancreatic sympathetic

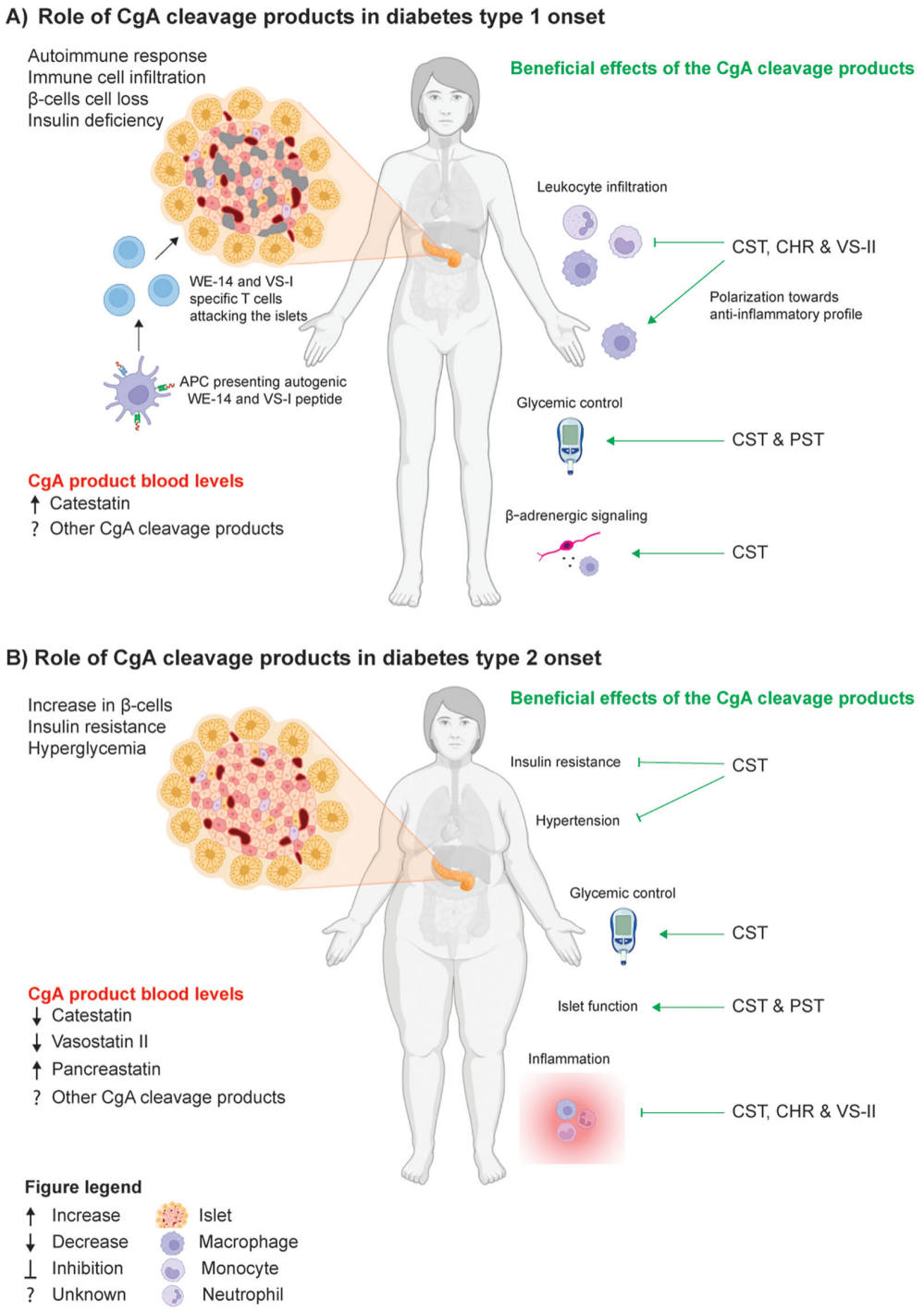

FIGURE 1
The role of CgA cleavage products in diabetes onset. **(A)** Diabetes type 1 (T1D) is characterized with an autoimmune response which results in islet immune cell infiltration (incl. autogenic WE-14 and vasostatin (VS)-I T cells), β-cell loss and insulin deficiency. Individuals with T1D display high catestatin (CST) blood levels, but the levels of other CgA cleavage products are currently unknown. Beneficial effects of the CgA cleavage products (in green) are observed on 1) leukocyte infiltration and macrophage polarization by CST, chromofungin (CHR) and VS-II 2) Glycemic control by CST and pancreastatin (PST) 3) Interference in nerve-immune communication via β-adrenergic signaling by CST **(B)** Diabetes type 2 (T2D) is characterized with an increase in β-cells, insulin resistance and hyperglycaemia. Individuals with T2D display low CST and VS-II, but high PST blood levels. Beneficial effects of the CgA cleavage products (in green) are observed on 1) insulin resistance and hypertension via CST 2) Glycemic control by CST 3) Endocrine islet function by CST and PST 4) Inflammation via CST, CHR and VS-II (partly created with BioRender).

innervation (80) or neuronal activity to pancreatic draining lymph nodes limits disease onset (84). Some of these effects have been hypothesized to be linked to neurotransmitter input to macrophages (80). The densities of sympathetic nerves and macrophages are not affected in the CST-KO mice. However, nerve-macrophage interactions seem to be less frequent upon CgA or CST deletion (43). CST is known to inhibit catecholamine release as shown on rat PC12 pheochromocytoma

cells (cell line from an adrenal gland tumor), primary cultures of adrenal chromaffin cells and noradrenergic neurites (85). In line with this, CST-KO mice display increased plasma levels of catecholamines when compared to WT mice (43). Since pancreatic islets produce CST, this might act as a local regulator of catecholamine release from islet neurons.

At T1D onset, the release of catecholamines from the adrenal gland into the plasma is disturbed which negatively affects glycemic control (86). Since CST levels are high at early T1D disease, CST might play a role here by inhibiting release or affecting the breakdown of catecholamines.

Altogether it seems that CST may exert some of its effects on diabetes onset via a complex nerve-macrophage-endocrine interplay where the control of catecholamine levels plays a key role. Low CST levels result in high catecholamine levels contributing to insulin resistance and hypertension as observed in T2D (38, 75, 76, 87). In contrast, increased CST levels, lower catecholamine levels and elevated nerve growth factor (NGF) levels are observed in T1D (4, 43, 88), which could contribute to increased insulin sensitivity and loss of homeostasis by disruption of nerve-immune communication. However, more research would be necessary to be able to define the effects of CST on catecholamine levels and its contribution to nerve-immune communication in T1D onset. Additionally, the interplay of other CgA cleavage products that can affect macrophages such as PST and CHR should be investigated.

2.6 Bioactive CgA derived peptide receptors to execute their physiological function

Although our understanding of the functions of CgA-derived peptides increases, the studies and knowledge on their receptors are still limited.

The peptides CHR and CST can penetrate the bacterial cell wall directly to execute their antibacterial and antifungal function (32, 39, 89). VS-I/II working mechanism seems to include phosphoinositide 3-kinase-dependent eNOS phosphorylation by binding to the cell membrane via phosphatidylserine or other membrane-relevant phospholipids, heparan sulfate proteoglycans and/or neuropilin-1 (90–92). For serpinin there are hints that it executes its effect via a GPCR since it triggers cAMP formation and/or a β1-adrenergic receptor (56, 59). CST has a broad variety of functions and seems to execute its function via muscarinic and nicotinic acetyl choline receptors, G-protein coupled receptors and potentially β-adrenergic receptors (42, 85, 93–97). Since PST has opposite effects of CST it might bind similar receptors, but so far it seems that PST binds glucose regulated protein 78 (GRP78) as well as G-protein coupled receptors, $G\alpha_{q/11}$ and $G\alpha_{i1,2}$ (98–100).

In summary, the CgA derived peptides seem to use two mechanisms of action to execute their physiological function. They either penetrate or bind directly to the cell membrane as observed for VS-I/II, CHR and CST (32, 39, 89–92) and/or they bind receptors on the cell surface as seen for serpinin, CST and PST (42, 56, 59, 85, 93–100). Since the physiological function of the peptides have such a wide range of effects, the bioactive peptides might use several different receptors in both potentiating and antagonizing fashions to execute their functions.

2.7 Therapeutic potential of CgA cleavage products in diabetes treatment

2.7.1 CgA cleavage product supplementation as medication

Although CST is not approved to use as a treatment in the clinic yet, the findings presented above positions it as a potential treatment avenue for patients with diabetes (Figure 1). We know that the administration of CST or PST is not harmful for healthy or diabetic individuals (34, 37). It is also known that hypertension and even changes in islet morphology are reversible upon normalizing blood glucose levels as shown by anti-diabetic drug (insulin or glibenclamide) treatment of bV59M mice, with β-cell dysfunction exposed to long-term hyperglycaemia (101).

Normal CST is not stable for peroral administration, however the analogue retro-inverso (R-I) CST or the CST analogue TKO-10–18 have peroral bioavailability and activity as tested for hypertension and diabetes (102, 103).

2.7.2 Inhibitors of CgA cleavage products as medication

Instead of CST supplementation, it could be beneficial to block CST or PST levels/function as a treatment for individuals with diabetes. A promising drug to block PST function is PSTi8, which seems most effective when administered in low doses for a longer period of time. PSTi8 competes with PST for binding on the GRP78 receptor resulting in enhanced insulin sensitivity and improved glucose homeostasis in mouse models for obesity and T2D (HFD, HFrD and db/db) (104, 105). The autoantigenicity of WE-14 and serpinin could be used to develop better antigen-specific immunotherapy for individuals with T1D or at high risk of developing T1D (106, 107). Altogether, CgA peptides seem promising for the development of new medication for individuals with diabetes. However, more research is necessary to determine the therapeutic potential of CgA cleavage products and inhibitors in humans.

3 Discussion

Although the field mostly used mouse models, it is increasingly clear that CgA and its cleavage products are crucial for controlling body homeostasis (Figure 1). The lack of certain CgA cleavage products seems to drive important parts of the development of T1D and T2D. Although the field made important discoveries in the past 10 years, the following questions remain to be answered in the future 1) How can we translate the finding from mouse to human? 2) Is it only the lack of the autoantigens (WE-14 and VS-1) that protect CgA-KO NOD mice from the development of autoimmune diabetes? 3) How do the reported inflammatory effects of PST and anti-inflammatory effects of CHR as well as CST contribute to the onset of T1D and T2D? 4) How do the organ and blood levels of all known CgA cleavage

products elevate during T1D and T2D development and how are they regulated? What are the pathways and receptors involved in executing their beneficial effects? To answer these questions. future research should include human research using for example plasma samples, human derived islets and clinical studies. Understanding the exact role and balance of CgA cleavage product levels in diabetes progression would help to develop diagnostic assays to follow disease progression and possible treatments by blocking or supplementing CgA cleavage products to treat diabetes in the future.

Author contributions

GC: Writing – review & editing. EM: Writing – review & editing, Writing – original draft.

Funding

The author(s) declared that financial support was received for this work and/or its publication. EM is funded by the Swedish Research Council (2023–05647) and O.E. och Edla Johanssons vetenskapliga stiftelse. G.C. is supported by grants from the Swedish Research Council (2018-02314 and 2023-02900), the Swedish Society for Medical Research, the Child Diabetes Foundation, and the Göran Gustafsson Foundation.

Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declared that generative AI was not used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Mahata SK, Corti A. Chromogranin a and its fragments in cardiovascular, immunometabolic, and cancer regulation. *Ann N Y Acad Sci*. (2019) 1455:34–58. doi: 10.1111/nyas.14249

2. Yu H, Wang H, Su X, Cao A, Yao X, Wang Y, et al. Serum chromogranin a correlated with albuminuria in diabetic patients and is associated with early diabetic nephropathy. *BMC Nephrol*. (2022) 23:41. doi: 10.1186/s12882-022-02667-0

3. Soell M, Feki A, Hannig M, Sano H, Pinget M, Selimović D. Chromogranin a detection in saliva of type 2 diabetes patients. *Biomol BioMed*. (2010) 10:2–6. doi: 10.17305/bjbms.2010.2725

4. Ochocińska A, Wysocka-Mincewicz M, Świderska J, Cukrowska B. Selected serum markers associated with pathogenesis and clinical course of type 1 diabetes in pediatric patients-the effect of disease duration. *J Clin Med*. (2023) 12:2151. doi: 10.3390/jcm12062151

5. Kogawa EM, Grisi DC, Falcão DP, Amorim IA, Rezende TMB, da Silva ICR, et al. Salivary function impairment in type 2 diabetes patients associated with concentration and genetic polymorphisms of chromogranin a. *Clin Oral Investig*. (2016) 20:2083–95. doi: 10.1007/s00784-015-1705-z

6. Ioannidis M, van Dijk H, Muntjewerff EM, Chirasani VR, Warner H, van den Dool W, et al. Inflammation promotes proteolytic processing of the prohormone chromogranin a by macrophages. *J Endocr Soc*. (2025) 9:bvaf090. doi: 10.1210/jendso/bvaf090

7. Muntjewerff EM, Dunkel G, Nicolasen MJT, Mahata SK, van den Bogaart G. Catestatin as a target for treatment of inflammatory diseases. *Front Immunol*. (2018) 9:2199. doi: 10.3389/fimmu.2018.02199

8. Maj M, Hernik K, Tyszkiewicz K. A complex role of chromogranin a and its peptides in inflammation, autoimmunity, and infections. (2025) 16:1–15. doi: 10.3389/fimmu.2025.1567874

9. Wen G, Mahata SK, Cadman P, Mahata M, Ghosh S, Mahapatra NR, et al. Both rare and common polymorphisms contribute functional variation at CHGA, a regulator of catecholamine physiology. *Am J Hum Genet*. (2004) 74:197–207. doi: 10.1086/381399

10. Marjani A, Pursharifi N, Sajedi A, Tatari M. Age and sex-related chromogranin a gene polymorphisms and its association with metabolic syndrome components. *J ASEAN Fed Endocr Soc*. (2024) 39:45–52. doi: 10.15605/jafes.039.01.09

11. Chen Y, Rao F, Rodriguez-Flores JL, Mahata M, Fung MM, Stridsberg M, et al. Naturally occurring human genetic variation in the 3′-untranslated region of the secretory protein chromogranin a is associated with autonomic blood pressure regulation and hypertension in a sex-dependent fashion. *J Am Coll Cardiol*. (2008) 52:1468–81. doi: 10.1016/j.jacc.2008.07.047

12. Chen Y, Rao F, Rodriguez-Flores JL, Mahapatra NR, Mahata M, Wen G, et al. Common genetic variants in the chromogranin a promoter alter autonomic activity and blood pressure. *Kidney Int*. (2008) 74:115–25. doi: 10.1038/ki.2008.113

13. Salem RM, Cadman PE, Chen Y, Rao F, Wen G, Hamilton BA, et al. Chromogranin a polymorphisms are associated with hypertensive renal disease. *J Am Soc Nephrol*. (2008) 19:600–14. doi: 10.1681/ASN.2007070754

14. Lillie EO, Mahata M, Khandrika S, Rao F, Bundey RA, Wen G, et al. Heredity of endothelin secretion. *Circulation*. (2007) 115:2282–91. doi: 10.1161/CIRCULATIONAHA.106.648345

15. Chen Y, Rao F, Wen G, Gayen JR, Zhang K, Vaingankar SM, et al. Naturally occurring genetic variants in human chromogranin a (CHGA) associated with hypertension as well as hypertensive renal disease. *Cell Mol Neurobiol*. (2010) 30:1395–400. doi: 10.1007/s10571-010-9600-2

16. Allu PKR, Kiranmayi M, Mukherjee SD, Chirasani VR, Garg R, Vishnuprabu D, et al. Functional Gly297Ser variant of the physiological dysglycemic peptide pancreastatin is a novel risk factor for cardiometabolic disorders. *Diabetes*. (2022) 71:538–53. doi: 10.2337/db21-0289

17. Corti A, Marcucci F, Bachetti T. Circulating chromogranin a and its fragments as diagnostic and prognostic disease markers. *Pflügers Arch - Eur J Physiol*. (2018) 470:199–210. doi: 10.1007/s00424-017-2030-y

18. De Block CEM, Colpin G, Thielemans K, Coopmans W, Bogers JJPM, Pelckmans PA, et al. Neuroendocrine tumor markers and enterochromaffin-like cell hyper/dysplasia in type 1 diabetes. *Diabetes Care*. (2004) 27:1387–93. doi: 10.2337/diacare.27.6.1387

19. Xiong W, Wang X, Dai D, Zhang B, Lu L, Tao R. The anti-inflammatory vasostatin-2 attenuates atherosclerosis in ApoE(-/-) mice and inhibits monocyte/macrophage recruitment. *Thromb Haemost*. (2017) 117:401–14. doi: 10.1160/TH16-06-0475

20. Bao XL, Dai Y, Lu L, Wang XQ, Ding FH, Shen WF, et al. Vasostatin-2 associates with coronary collateral vessel formation in diabetic patients and promotes angiogenesis via angiotensin-converting enzyme 2. *Eur Heart J*. (2023) 44:1732–44. doi: 10.1093/eurheartj/ehad082

21. Lu L, Wang YN, Li MC, Wang HB, Pu LJ, Niu WQ, et al. Reduced serum levels of vasostatin-2, an anti-inflammatory peptide derived from chromogranin a, are associated with the presence and severity of coronary artery disease. *Eur Heart J*. (2012) 33:2297–306. doi: 10.1093/eurheartj/ehs122

22. Crippa L, Bianco M, Colombo B, Gasparri AM, Ferrero E, Loh YP, et al. A new chromogranin a–dependent angiogenic switch activated by thrombin. *Blood*. (2013) 121:392–402. doi: 10.1182/blood-2012-05-430314

23. Nikoopour E, Cheung R, Bellemore S, Krougly O, Lee-Chan E, Stridsberg M, et al. Vasostatin-1 antigenic epitope mapping for induction of cellular and humoral immune responses to chromogranin <scp>A</scp> autoantigen in <scp>NOD</scp> mice. *Eur J Immunol*. (2014) 44:1170–80. doi: 10.1002/eji.201343986

24. Ives AN, Sagendorf TJ, Nierves L, Lin T-T, Dirice E, Kulkarni RN, et al. Characterization of cytokine treatment on human pancreatic islets by top-down proteomics. *Proteomics*. (2025) 25:55–66. doi: 10.1002/pmic.70044

25. Nikoopour E, Krougly O, Lee-Chan E, Haeryfar SM, Singh B. Detection of vasostatin-1-specific CD8+ T cells in non-obese diabetic mice that contribute to diabetes pathogenesis. *Clin Exp Immunol*. (2016) 185:292–300. doi: 10.1111/cei.12811

26. Nikoopour E, Sandrock C, Huszarik K, Krougly O, Lee-Chan E, Masteller EL, et al. Cutting edge: Vasostatin-1–derived peptide ChgA29–42 is an antigenic epitope of diabetogenic BDC2.5 T cells in nonobese diabetic mice. *J Immunol*. (2011) 186:3831–5. doi: 10.4049/jimmunol.1003617

27. Li Y, Zhou L, Li Y, Zhang J, Guo B, Meng G, et al. Identification of autoreactive CD8+ T cell responses targeting chromogranin a in humanized NOD mice and type 1 diabetes patients. *Clin Immunol*. (2015) 159:63–71. doi: 10.1016/j.clim.2015.04.017

28. Eissa N, Hussein H, Kermarrec L, Grover J, Metz-Boutigue M-H, Bernstein CN, et al. Chromofungin ameliorates the progression of colitis by regulating alternatively activated macrophages. *Front Immunol*. (2017) 8:1131. doi: 10.3389/fimmu.2017.01131

29. Eissa N, Hussein H, Kermarrec L, Elgazzar O, Metz-Boutigue M-H, Bernstein CN, et al. Chromofungin (CHR: CHGA47-66) is downregulated in persons with active ulcerative colitis and suppresses pro-inflammatory macrophage function through the inhibition of NF-κB signaling. *Biochem Pharmacol*. (2017) 145:102–13. doi: 10.1016/j.bcp.2017.08.013

30. Filice E, Pasqua T, Quintieri AM, Cantafio P, Scavello F, Amodio N, et al. Chromofungin, CgA47-66-derived peptide, produces basal cardiac effects and postconditioning cardioprotective action during ischemia/reperfusion injury. *Peptides*. (2015) 71:40–8. doi: 10.1016/j.peptides.2015.06.013

31. Tota B, Mazza R, Angelone T, Nullans G, Metz-Boutigue M-H, Aunis D, et al. Peptides from the N-terminal domain of chromogranin a (vasostatins) exert negative inotropic effects in the isolated frog heart. *Regul Pept*. (2003) 114:123–30. doi: 10.1016/S0167-0115(03)00112-5

32. Lugardon K, Chasserot-Golaz S, Kieffer A-E, Maget-Dana R, Nullans G, Kieffer B, et al. Structural and biological characterization of chromofungin, the antifungal chromogranin a-(47–66)-derived peptide*. *J Biol Chem*. (2001) 276:35875–82. doi: 10.1074/jbc.M104670200

33. Zhang D, Shooshtarizadeh P, Laventie B-J, Colin DA, Chich J-F, Vidic J, et al. Two chromogranin a-derived peptides induce calcium entry in human neutrophils by calmodulin-regulated calcium independent phospholipase a2. *PloS One*. (2009) 4: e4501. doi: 10.1371/journal.pone.0004501

34. O'Connor DT, Cadman PE, Smiley C, Salem RM, Rao F, Smith J, et al. Pancreastatin: Multiple actions on human intermediary metabolism *in vivo*, variation in disease, and naturally occurring functional genetic polymorphism. *J Clin Endocrinol Metab*. (2005) 90:5414–25. doi: 10.1210/jc.2005-0408

35. Unal Kocabas G, Yildirim Simsir I, Sarer Yurekli B, Suner Karakulah A, Durmaz B, Pehlivan Koroglu E, et al. The association of plasma pancreastatin levels with insulin resistance in patients with gestational diabetes mellitus. *Obstet Med*. (2024) 17:221–5. doi: 10.1177/1753495X231216032

36. Sánchez-Margalet V, Lobón JA, González A, Fernández-Soto ML, Escobar-Jiménez F, Goberna R. Increased plasma pancreastatin-like levels in gestational diabetes: correlation with catecholamine levels. *Diabetes Care*. (1998) 21:1951–4. doi: 10.2337/diacare.21.11.1951

37. Funakoshi A, Tateishi K, Shinozaki H, Wakasugi H. Elevated plasma levels of pancreastatin (PST) in patients with non-insulin-dependent diabetes mellitus (NIDDM). *Regul Pept*. (1990) 30:159–64. doi: 10.1016/0167-0115(90)90056-3

38. Pankova O, Korzh O. Plasma catestatin levels are related to metabolic parameters in patients with essential hypertension and type 2 diabetes mellitus. *Heart Vessels*. (2024) 39:144–59. doi: 10.1007/s00380-023-02318-w

39. Radek KA, Lopez-Garcia B, Hupe M, Niesman IR, Elias PM, Taupenot L, et al. The neuroendocrine peptide catestatin is a cutaneous antimicrobial and induced in the skin after injury. *J Invest Dermatol*. (2008) 128:1525–34. doi: 10.1038/sj.jid.5701225

40. Aung G, Niyonsaba F, Ushio H, Kajiwara N, Saito H, Ikeda S, et al. Catestatin, a neuroendocrine antimicrobial peptide, induces human mast cell migration, degranulation and production of cytokines and chemokines. *Immunology*. (2011) 132:527–39. doi: 10.1111/j.1365-2567.2010.03395.x

41. Theurl M, Schgoer W, Albrecht K, Jeschke J, Egger M, Beer AGE, et al. The neuropeptide catestatin acts as a novel angiogenic cytokine via a basic fibroblast growth factor–dependent mechanism. *Circ Res*. (2010) 107:1326–35. doi: 10.1161/CIRCRESAHA.110.219493

42. Muntjewerff EM, Parv K, Mahata SK, van Riessen NK, Phillipson M, Christoffersson G, et al. The anti-inflammatory peptide catestatin blocks chemotaxis. *J Leukoc Biol*. (2022) 112:273–8. doi: 10.1002/JLB.3CRA1220-790RR

43. Muntjewerff EM, Epremidze D, Nezhyva M, Kal S, Rohm TV, Tang K, et al. Chromogranin a and catestatin regulate pancreatic islet homeostasis, endocrine function, and neurotransmitter signaling. *Commun Biol*. (2025) 8:1684. doi: 10.1038/s42003-025-09135-z

44. Bassino E, Fornero S, Gallo MP, Ramella R, Mahata SK, Tota B, et al. A novel catestatin-induced antiadrenergic mechanism triggered by the endothelial PI3K-eNOS pathway in the myocardium. *Cardiovasc Res*. (2011) 91:617–24. doi: 10.1093/cvr/cvr129

45. Montero-Hadjadje M, Vaudry H, Turquier V, Leprince J, Do Rego J-L, Yon L, et al. Localization and characterization of evolutionarily conserved chromogranin a-derived peptides in the rat and human pituitary and adrenal glands. *Cell Tissue Res*. (2002) 310:223–36. doi: 10.1007/s00441-002-0625-9

46. Guillemot J, Guérin M, Thouënnon E, Montéro-Hadjadje M, Leprince J, Lefebvre H, et al. Characterization and plasma measurement of the WE-14 peptide in patients with pheochromocytoma. *PloS One*. (2014) 9:e88698. doi: 10.1371/journal.pone.0088698

47. Delong T, Baker RL, He J, Barbour G, Bradley B, Haskins K. Diabetogenic T-cell clones recognize an altered peptide of chromogranin a. *Diabetes*. (2012) 61:3239–46. doi: 10.2337/db12-0112

48. Gottlieb PA, Delong T, Baker RL, Fitzgerald-Miller L, Wagner R, Cook G, et al. Chromogranin a is a T cell antigen in human type 1 diabetes. *J Autoimmun*. (2014) 50:38–41. doi: 10.1016/j.jaut.2013.10.003

49. Liu B, Hood JD, Kolawole EM, Woodruff DM, Vignali DA, Bettini M, et al. A hybrid insulin epitope maintains high 2D affinity for diabetogenic T cells in the periphery. *Diabetes*. (2020) 69:381–91. doi: 10.2337/db19-0399

50. Callebaut A, Guyer P, Baker RL, Gallegos JB, Hohenstein AC, Gottlieb PA, et al. An insulin-chromogranin a hybrid peptide activates DR11-restricted T cells in human type 1 diabetes. *Diabetes*. (2024) 73:743–50. doi: 10.2337/db23-0622

51. Delong T, Wiles TA, Baker RL, Bradley B, Barbour G, Reisdorph R, et al. Pathogenic CD4 T cells in type 1 diabetes recognize epitopes formed by peptide fusion. *Science*. (2016) 351:711–4. doi: 10.1126/science.aad2791

52. Reed B, Crawford F, Hill RC, Jin N, White J, Krovi SH, et al. Lysosomal cathepsin creates chimeric epitopes for diabetogenic CD4 T cells via transpeptidation. *J Exp Med*. (2021) 218:e20192135. doi: 10.1084/jem.20192135

53. Jin N, Wang Y, Crawford F, White J, Marrack P, Dai S, et al. N-terminal additions to the WE14 peptide of chromogranin A create strong autoantigen agonists in type 1 diabetes. *Proc Natl Acad Sci USA*. (2015) 112:13318–23. doi: 10.1073/pnas.1517862112

54. Baker RL, Jamison BL, Wiles TA, Lindsay RS, Barbour G, Bradley B, et al. CD4 T cells reactive to hybrid insulin peptides are indicators of disease activity in the NOD mouse. *Diabetes*. (2018) 67:1836–46. doi: 10.2337/db18-0200

55. Imbrogno S, Mazza R, Pugliese C, Filice M, Angelone T, Loh YP, et al. The chromogranin A-derived sympathomimetic serpinin depresses myocardial performance in teleost and amphibian hearts. *Gen Comp Endocrinol*. (2017) 240:1–9. doi: 10.1016/j.ygcen.2016.09.004

56. Tota B, Gentile S, Pasqua T, Bassino E, Koshimizu H, Cawley NX, et al. The novel chromogranin A-derived serpinin and pyroglutaminated serpinin peptides are positive cardiac β-adrenergic-like inotropes. *FASEB J*. (2012) 26:2888–98. doi: 10.1096/fj.11-201111

57. Loh YP, Koshimizu H, Cawley NX, Tota B. Serpinins: Role in granule biogenesis, inhibition of cell death and cardiac function. (2012) 19(24):4086–92. doi: 10.2174/092986712802429957

58. Koshimizu H, Cawley NX. Role of pGlu-Serpinin, a novel chromogranin A-derived peptide in inhibition of cell death. (2011) 45:294–303. doi: 10.1007/s12031-011-9521-7

59. Koshimizu H, Cawley NX, Kim T, Yergey AL, Loh YP. Serpinin: A novel chromogranin A-derived, secreted peptide up-regulates protease nexin-1 expression and granule biogenesis in endocrine cells. *Mol Endocrinol*. (2011) 25:732–44. doi: 10.1210/me.2010-0124

60. Pasqua T, Tota B, Penna C, Corti A, Cerra MC, Loh YP, et al. pGlu-serpinin protects the normotensive and hypertensive heart from ischemic injury. *J Endocrinol*. (2015) 227:167–78. doi: 10.1530/JOE-15-0199

61. Cappello S, Angelone T, Tota B, Pagliaro P, Penna C, Rastaldo R, et al. Human recombinant chromogranin A-derived vasostatin-1 mimics preconditioning via an adenosine/nitric oxide signaling mechanism. *Am J Physiol Circ Physiol*. (2007) 293: H719–27. doi: 10.1152/ajpheart.01352.2006

62. Gallo MP, Levi R, Ramella R, Brero A, Boero O, Tota B, et al. Endothelium-derived nitric oxide mediates the antiadrenergic effect of human vasostatin-1 in rat ventricular myocardium. *Am J Physiol Circ Physiol*. (2007) 292:H2906–12. doi: 10.1152/ajpheart.01253.2006

63. Fraquelli C, Hauzinger J, Humpel C, Nolano M, Provitera V, Sharma VK, et al. Serpinin in the skin. *Biomedicines*. (2022) 10:183. doi: 10.3390/biomedicines10010183

64. Rahman AA, Shahid IZ, Fong AY, Hammond AM, Pilowsky PM. Vasostatin I (CgA17-76) vasoconstricts rat splanchnic vascular bed but does not affect central cardiovascular function. *Auton Neurosci*. (2012) 166:22–8. doi: 10.1016/j.autneu.2011.08.023

65. Mahapatra NR, O'Connor DT, Vaingankar SM, Hikim APS, Mahata M, Ray S, et al. Hypertension from targeted ablation of chromogranin A can be rescued by the human ortholog. *J Clin Invest*. (2005) 115:1942–52. doi: 10.1172/JCI24354

66. Portela-Gomes GMM, Gayen JRR, Grimelius L, Stridsberg M, Mahata SKK. The importance of chromogranin A in the development and function of endocrine pancreas. *Regul Pept*. (2008) 151:19–25. doi: 10.1016/j.regpep.2008.07.005

67. Dev NB, Gayen JR, O'Connor DT, Mahata SK. Chromogranin a and the autonomic system: decomposition of heart rate variability and rescue by its catestatin fragment. *Endocrinology*. (2010) 151:2760–8. doi: 10.1210/en.2009-1110

68. Gayen JR, Saberi M, Schenk S, Biswas N, Vaingankar SM, Cheung WW, et al. A novel pathway of insulin sensitivity in chromogranin A null mice. *J Biol Chem*. (2009) 284:28498–509. doi: 10.1074/jbc.M109.020636

69. Gayen JR, Zhang K, RamachandraRao SP, Mahata M, Chen Y, Kim H-S, et al. Role of reactive oxygen species in hyperadrenergic hypertension. *Circ Cardiovasc Genet*. (2010) 3:414–25. doi: 10.1161/CIRCGENETICS.109.924050

70. Gayen JR, Saberi M, Schenk S, Biswas N, Vaingankar SM, Cheung WW, et al. A novel pathway of insulin sensitivity in chromogranin A null mice: a crucial role for pancreastatin in glucose homeostasis. *J Biol Chem*. (2009) 284:28498–509. doi: 10.1074/jbc.M109.020636

71. Tang K, Pasqua T, Biswas A, Mahata S, Tang J, Tang A, et al. Muscle injury, impaired muscle function and insulin resistance in chromogranin A-knockout mice. *J Endocrinol*. (2017) 232:137–53. doi: 10.1530/JOE-16-0370

72. Bandyopadhyay GK, Lu M, Avolio E, Siddiqui JA, Gayen JR, Wollam J, et al. Pancreastatin-dependent inflammatory signaling mediates obesity-induced insulin resistance. *Diabetes*. (2015) 64:104–16. doi: 10.2337/db13-1747

73. Baker RL, Bradley B, Wiles TA, Lindsay RS, Barbour G, Delong T, et al. Cutting edge: Nonobese diabetic mice deficient in chromogranin A are protected from autoimmune diabetes. *J Immunol*. (2016) 196:39–43. doi: 10.4049/jimmunol.1501190

74. Srivastava N, Hu H, Vomund AN, Peterson OJ, Baker RL, Haskins K, et al. Chromogranin A deficiency confers protection from autoimmune diabetes via multiple mechanisms. *Diabetes*. (2021) 70:2860–70. doi: 10.2337/db21-0513

75. Ying W, Tang K, Avolio E, Schilling JM, Pasqua T, Liu MA, et al. Immunosuppression of macrophages underlies the cardioprotective effects of CST (catestatin). *Hypertens (Dallas Tex 1979)*. (2021) 77:1670–82. doi: 10.1161/HYPERTENSIONAHA.120.16809

76. Ying W, Mahata S, Bandyopadhyay GK, Zhou Z, Wollam J, Vu J, et al. Catestatin inhibits obesity-induced macrophage infiltration and inflammation in the liver and suppresses hepatic glucose production, leading to improved insulin sensitivity. *Diabetes*. (2018) 67:841–8. doi: 10.2337/db17-0788

77. Muntjewerff EM, Tang K, Lutter L, Christoffersson G, Nicolasen MJT, Gao H, et al. Chromogranin A regulates gut permeability via the antagonistic actions of its proteolytic peptides. *Acta Physiol*. (2021) 232:e13655. doi: 10.1111/apha.13655

78. Sluga N, Križančić Bombek L, Kerčmar J, Sarikas S, Postić S, Pfabe J, et al. Physiological levels of adrenaline fail to stop pancreatic beta cell activity at unphysiologically high glucose levels. *Front Endocrinol (Lausanne)*. (2022) 13:1013697. doi: 10.3389/fendo.2022.1013697

79. Strubbe JH, Steffens AB. Neural control of insulin secretion. *Horm Metab Res*. (1993) 25:507–12. doi: 10.1055/s-2007-1002162

80. Christoffersson G, Ratliff SS, von Herrath MG. Interference with pancreatic sympathetic signaling halts the onset of diabetes in mice. *Sci Adv*. (2020) 6:Adv.6, eabb2878. doi: 10.1126/sciadv.abb2878

81. Muntjewerff EM, Christoffersson G, Mahata SK, van den Bogaart G. Putative regulation of macrophage-mediated inflammation by catestatin. *Trends Immunol*. (2022) 43:41–50. doi: 10.1016/j.it.2021.11.002

82. Mundinger TO, Mei Q, Foulis AK, Fligner CL, Hull RL, Taborsky GJ. Human type 1 diabetes is characterized by an early, marked, sustained, and islet-selective loss of sympathetic nerves. *Diabetes*. (2016) 65:2322–30. doi: 10.2337/db16-0284

83. Campbell-Thompson M, Butterworth EA, Boatwright JL, Nair MA, Nasif LH, Nasif K, et al. Islet sympathetic innervation and islet neuropathology in patients with type 1 diabetes. *Sci Rep*. (2021) 11:6562. doi: 10.1038/s41598-021-85659-8

84. Guyot M, Simon T, Ceppo F, Panzolini C, Guyon A, Lavergne J, et al. Pancreatic nerve electrostimulation inhibits recent-onset autoimmune diabetes. *Nat Biotechnol*. (2019) 37:1446–51. doi: 10.1038/s41587-019-0295-8

85. Mahata SK, O'Connor DT, Mahata M, Yoo SH, Taupenot L, Wu H, et al. Novel autocrine feedback control of catecholamine release. A discrete chromogranin a fragment is a noncompetitive nicotinic cholinergic antagonist. *J Clin Invest*. (1997) 100:1623–33. doi: 10.1172/JCI119686

86. de Galan BE, Tack CJ, Willemsen JJ, Sweep CGJ, Smits P, Lenders JWM. Plasma metanephrine levels are decreased in type 1 diabetic patients with a severely impaired epinephrine response to hypoglycemia, indicating reduced adrenomedullary stores of epinephrine. *J Clin Endocrinol Metab*. (2004) 89:2057–61. doi: 10.1210/jc.2003-031289

87. Ahrițculesei RV, Boldeanu L, Assani M-Z, Mitrea A, Obleaga CV, Vladu IM, et al. Neurotransmitter levels (dopamine, epinephrine, norepinephrine, serotonin) and associations with lipid profiles in patients with prediabetes or newly diagnosed type 2 diabetes mellitus. *Int J Mol Sci*. (2025) 26:10068. doi: 10.3390/ijms262010068

88. Heyman E, Delamarche P, Berthon P, Meeusen R, Briard D, Vincent S, et al. Alteration in sympathoadrenergic activity at rest and during intense exercise despite normal aerobic fitness in late pubertal adolescent girls with type 1 diabetes. *Diabetes Metab*. (2007) 33:422–9. doi: 10.1016/j.diabet.2007.10.003

89. Scavello F, Mutschler A, Hellé S, Schneider F, Chasserot-Golaz S, Strub J-M, et al. Catestatin in innate immunity and Cateslytin-derived peptides against superbugs. *Sci Rep*. (2021) 11:15615. doi: 10.1038/s41598-021-94749-6

90. Blois A, Holmsen H, Martino G, Corti A, Metz-Boutigue M-H, Helle KB. Interactions of chromogranin A-derived vasostatins and monolayers of phosphatidylserine, phosphatidylcholine and phosphatidylethanolamine. *Regul Pept*. (2006) 134:30–7. doi: 10.1016/j.regpep.2005.11.003

91. Ramella R, Boero O, Alloatti G, Angelone T, Levi R, Gallo MP. Vasostatin 1 activates eNOS in endothelial cells through a proteoglycan-dependent mechanism. *J Cell Biochem*. (2010) 110:70–9. doi: 10.1002/jcb.22510

92. Belloni D, Scabini S, Foglieni C, Veschini L, Giazzon A, Colombo B, et al. The vasostatin-I fragment of chromogranin A inhibits VEGF-induced endothelial cell proliferation and migration. *FASEB J*. (2007) 21:3052–62. doi: 10.1096/fj.06-6829com

93. Taupenot L, Mahata SK, Mahata M, Parmer RJ, O'Connor DT. Interaction of the catecholamine release-inhibitory peptide catestatin (human chromogranin A352-372) with the chromaffin cell surface and Torpedo electroplax: implications for nicotinic cholinergic antagonism. *Regul Pept*. (2000) 95:9–17. doi: 10.1016/S0167-0115(00)00135-X

94. Tsigelny I, Mahata SK, Taupenot L, Preece NE, Mahata M, Khan I, et al. Mechanism of action of chromogranin A on catecholamine release: molecular modeling of the catestatin region reveals a β-strand/loop/β-strand structure secured by hydrophobic interactions and predictive of activity. *Regul Pept*. (1998) 77:43–53. doi: 10.1016/S0167-0115(98)00040-8

95. Liao F, Zheng Y, Cai J, Fan J, Wang J, Yang J, et al. Catestatin attenuates endoplasmic reticulum induced cell apoptosis by activation type 2 muscarinic acetylcholine receptor in cardiac ischemia/reperfusion. *Sci Rep*. (2015) 5:16590. doi: 10.1038/srep16590

96. Angelone T, Quintieri AM, Brar BK, Limchaiyawat PT, Tota B, Mahata SK, et al. The antihypertensive chromogranin A peptide catestatin acts as a novel endocrine/paracrine modulator of cardiac inotropism and lusitropism. *Endocrinology*. (2008) 149:4780–93. doi: 10.1210/en.2008-0318

97. Kiranmayi M, Chirasani VR, Allu PKR, Subramanian L, Martelli EE, Sahu BS, et al. Catestatin Gly364Ser variant alters systemic blood pressure and the risk for hypertension in human populations via endothelial nitric oxide pathway. *Hypertension*. (2016) 68:334–47. doi: 10.1161/HYPERTENSIONAHA.116.06568

98. Biswas N, Friese RS, Gayen JR, Bandyopadhyay G, Mahata SK, O'Connor DT. Discovery of a novel target for the dysglycemic chromogranin A fragment pancreastatin: interaction with the chaperone GRP78 to influence metabolism. *PloS One*. (2014) 9:e84132. doi: 10.1371/journal.pone.0084132

99. González-Yanes C, Santos-Alvarez J, Sánchez-Margalet V. Characterization of pancreastatin receptors and signaling in adipocyte membranes. *Biochim Biophys Acta Mol Cell Res*. (1999) 1451:153–62. doi: 10.1016/S0167-4889(99)00084-1

100. Santos-Álvarez J, González-Yanes C, Sánchez-Margalet V. Pancreastatin receptor is coupled to a guanosine triphosphate-binding protein of the Gg/11α family in rat liver membranes. *Hepatology*. (1998) 27:608–14. doi: 10.1002/hep.510270240

101. Brereton MF, Iberl M, Shimomura K, Zhang Q, Adriaenssens AE, Proks P, et al. Reversible changes in pancreatic islet structure and function produced by elevated blood glucose. *Nat Commun*. (2014) 5:4639. doi: 10.1038/ncomms5639

102. Biswas N, Gayen J, Mahata M, Su Y, Mahata SK, O'Connor DT. Novel peptide isomer strategy for stable inhibition of catecholamine release. *Hypertension*. (2012) 60:1552–9. doi: 10.1161/HYPERTENSIONAHA.112.202127

103. Tsigelny IF, Kouznetsova VL, Biswas N, Mahata SK, O'Connor DT. Development of a pharmacophore model for the catecholamine release-inhibitory peptide catestatin: Virtual screening and functional testing identify novel small molecule therapeutics of hypertension. *Bioorg Med Chem*. (2013) 21:5855–69. doi: 10.1016/j.bmc.2013.07.008

104. Hossain Z, Valicherla GR, Gupta AP, Syed AA, Riyazuddin M, Chandra S, et al. Discovery of pancreastatin inhibitor PSTi8 for the treatment of insulin resistance and diabetes: Studies in rodent models of diabetes mellitus. *Sci Rep*. (2018) 8:8715. doi: 10.1038/s41598-018-27018-8

105. Singh P, Garg R, Goand UK, Riyazuddin M, Reza MI, Syed AA, et al. Combination of pancreastatin inhibitor PSTi8 with metformin inhibits Fetuin-A in type 2 diabetic mice. *Heliyon*. (2020) 6:e05133. doi: 10.1016/j.heliyon.2020.e05133

106. Dastagir SR, Postigo-Fernandez J, Xu C, Stoeckle JH, Firdessa-Fite R, Creusot RJ. Efficient presentation of multiple endogenous epitopes to both $CD4^+$ and $CD8^+$ diabetogenic T cells for tolerance. *Mol Ther Methods Clin Dev*. (2017) 4:27–38. doi: 10.1016/j.omtm.2016.12.002

107. Zhao X, Birchall JC, Coulman SA, Tatovic D, Singh RK, Wen L, et al. Microneedle delivery of autoantigen for immunotherapy in type 1 diabetes. *J Control Release*. (2016) 223:178–87. doi: 10.1016/j.jconrel.2015.12.040