**Name of Journal:** *World Journal of Diabetes*

**Manuscript NO:** 63333

**Manuscript Type:** MINIREVIEWS

**Role and function of granin proteins in diabetes mellitus**

Herold Z *et al*. Role of granin proteins in diabetes

Zoltan Herold, Marton Doleschall, Aniko Somogyi

**Zoltan Herold,** Division of Oncology, Department of Internal Medicine and Oncology, Semmelweis University, Budapest 1083, Hungary

**Zoltan Herold, Aniko Somogyi,** Department of Internal Medicine and Hematology, Semmelweis University, Budapest 1088, Hungary

**Marton Doleschall,** Molecular Medicine Research Group, Eotvos Lorand Research Network and Semmelweis University, Budapest 1089, Hungary

**Author contributions:** Herold Z and Doleschall M searched the literature and drafted initial manuscript; Somogyi A provided further editing and comments; all authors have read and agreed to the published version of the manuscript.

**Supported by** theNew National Excellence Program of the Ministry for Innovation and Technology from the source of the National Research, Development and Innovation Fund, No. UNKP-20-4-I.

**Corresponding author: Zoltan Herold, MSc, Research Scientist,** Division of Oncology, Department of Internal Medicine and Oncology, Semmelweis University, Tomo u. 25-29, Budapest 1083, Hungary. herold.zoltan@med.semmelweis-univ.hu

**Received:** January 27, 2021

**Revised:** March 5, 2021

**Accepted:** May 17, 2021

**Published online:**

**Abstract**

The granin glycoprotein family consists of nine acidic proteins; chromogranin A (CgA), chromogranin B (CgB), and secretogranin II–VIII. They are produced by a wide range of neuronal, neuroendocrine, and endocrine cells throughout the human body. Their major intracellular function is to sort peptides and proteins into secretory granules, but their cleavage products also take part in the extracellular regulation of diverse biological processes. The contribution of granins to carbohydrate metabolism and diabetes mellitus is a recent research area. CgA is associated with glucose homeostasis and the progression of type 1 diabetes. WE-14, CgA10-19, and CgA43-52 are peptide derivates of CgA, and act as CD4+ or CD8+ autoantigens in type 1 diabetes, whereas pancreastatin (PST) and catestatin have regulatory effects in carbohydrate metabolism. Furthermore, PST is related to gestational and type 2 diabetes. CgB has a crucial role in physiological insulin secretion. Secretogranins II and III have angiogenic activity in diabetic retinopathy (DR), and are novel targets in recent DR studies. Ongoing studies are beginning to investigate the potential use of granin derivatives as drugs to treat diabetes based on the divergent relationships between granins and different types of diabetes.

**Key Words:** Granin; Chromogranin A; Chromogranin B; Diabetes Mellitus; Mice; Inbred nonobese diabetic; Secretogranin III

Herold Z, Doleschall M, Somogyi A. Role and function of granin proteins in diabetes mellitus. *World J Diabetes* 2021; In press

**Core Tip:** Granin glycoproteins are secretory proteins that are widely produced by neuronal, neuroendocrine, and endocrine cells throughout the human body. Recent data have shown that the granin proteins chromogranin A and B, and secretogranin II and III play a role in carbohydrate metabolism and in the pathophysiology of diabetes mellitus. In this review, the current state of knowledge concerning the relationship between granin proteins, diabetes and glucose homeostasis is discussed in detail, including several ongoing studies investigating granin-based drug therapies of future promise in diabetes care.

**INTRODUCTION**

Neuronal, neuroendocrine, and endocrine cells are involved in the production of many peptides and proteins with diverse functions. During the secretion of these biologically active molecules, secretory proteins play an important role in the protein sorting that takes place in the secretory vesicles of the Golgi apparatus. The members belonging to the granin glycoprotein family, chromogranin A (CgA), chromogranin B (CgB), and secretogranin (Sg) II–VIII (Table 1), participate in protein sorting[1]. Granin proteins all have an acidic pH, calcium-binding ability, and are produced throughout the body by several types of neuronal-, neuroendocrine-, and endocrine cells[1-4]. In addition to protein sorting, secondary functions that are related mainly to the cleavage products of the granin proteins (Table 2) have emerged during evolution. Some of these biologically active products have been described as participating in pathogen control, psychiatric disorders, and metabolic disorders such as diabetes mellitus[1,3,5-7]. The function of many other granin protein products is still unclear. The available literature on granin proteins and their cleavage products is discussed in this review, focusing on their relationships to diabetes mellitus and carbohydrate metabolism. The in-depth presentation of the biochemistry, genetics, distribution, and function of the various granin proteins is not the aim of the current review, but publications on those subjects are available[1,8-14].

**THE ROLE OF GRANINS IN THE SECRETION OF INSULIN**

The presence of CgA[15], CgB[16-18], SgII[15] and SgVII (*VGF*, non-acronymic)[19,20] as secretory proteins has been described in animal and cellular models of pancreatic islets. Pancreatic beta cells of chromogranin A gene (*CHGA*) knockout (KO) mice were reported to have compensatory overexpression of CgB and SgII, with simultaneous insulin overproduction and fewer immature secretory granules. The CgA cleavage products betagranin (CgA1-128)[21], vasostatin-I (CgA1-76) and catestatin (CST, CgA352-372) are found in beta cells; pancreastatin (PST, CgA250-301) is found in alpha cells[15,22], indicating different protein cleavage products mediated by different endoproteases[14].

Betagranin was reported to have a negative effect on glucose-stimulated insulin secretion (GSIS). Betagranin treatment of murine insulinoma cell lines was found to inhibit insulin secretion in a dose-dependent manner that was associated with dysfunction of the calcium response[21]. Normal cell function was restored when betagranin was removed. Antibodies against CgA or PST have no effect on insulin secretion, while the partial absence of CgB results in increased proinsulin synthesis[23]. Colocalization of insulin and CgB was confirmed in the *trans*-Golgi network of human and murine islet cells from healthy and insulinoma tissue[17]. Glucose-stimulated insulin, glucagon, and somatostatin secretion were decreased in chromogranin B gene (*CHGB)* KO mice in parallel with a decrease in the amount of circulating insulin and a slight decrease in renal glucose clearance. The insulin sensitivity of *CHGB* KO mice did not differ from that of wild-type mice[18]. Proinsulin processing was slowed in the absence of CgB. The density of proinsulin-containing secretory granules was altered, causing significantly slower detachment of these granules from the *trans*-Golgi network, which ultimately delayed the translocation of the granules to the plasma membrane. Although the function of cell surface receptors was not different from that of wild-type mice, the initial, rapid phase of GSIS was virtually absent in *CHGB* KO mice. The loss of rapid GSIS was compensated by increased basal insulin production, and the beta cells of *CHGB* KO mice stored and secreted twice as much proinsulin than the beta cells of wild-type mice[16,18]. These observations, seen in KO mice, are similar to the characteristics of type 2 diabetes mellitus (T2DM) in humans[18].Stimulus-coupled insulin secretion was decreased in *VGF* (the gene that encodes SgVII protein) KO mice. An impairment of the second phase of insulin secretion was described, and secretory granules detached significantly more slowly from the *trans*-Golgi network, and was accompanied by an increase in the proinsulin level[20], similar to the effect observed in the case of CgB.

**GRANIN PEPTIDES IN GLUCOSE HOMEOSTASIS**

***Pancreastatin***

PST negatively regulates insulin sensitivity and glucose homeostasis. PST-mediated inhibition of insulin secretion promotes a high blood glucose level (hyperglycemia). Moreover, PST can: (1) Reduce the hepatic glucose uptake through inhibiting the insulin-stimulated glycogenesis in primary hepatocytes; (2) Decrease the insulin-stimulated synthesis of lipids; and (3) Regulate the expression and secretion of leptin in adipocytes, which also increases blood glucose levels[24-27]. G-protein-activated phospholipase C β3 isoforms[5,28-30] or activation of nitric oxide pathways[31-33] in hepatocytes inhibit insulin but only the former pathway has been described in adipocytes[5,30]. *CHGA* KO mice are obese, have hypertension, diminished baroreflex sensitivity, increased plasma catecholamine and adipokine levels, and lower interleukin-6 and lipid levels compared with wild-type animals[32,34]. A normal blood glucose level (euglycemia) is maintained by increased liver insulin sensitivity in *CHGA* KO mice, which is supported by the abundance of hepatic phosphoenolpyruvate carboxykinase (PEPC) and glucose-6-phosphatase (G6Pase) mRNAs. *CHGA* KO mice treated with PST are euglycemic, even in the absence of PEPC and G6Pase mRNAs[32].

The PST inhibitor peptide-8 (PSTi8)[35-39] reduces the effects of PST-induced insulin resistance. PSTi8 increases translocation of glucose transporter type 4 to the cell surface in hepatocytes and adipocytes, thereby promoting glucose uptake. It also reduces hepatic glucose release, lipid deposition, dexamethasone-induced oxidative stress; stimulates hepatocellular energy levels, and enhances the activity of glucose response protein 78[37,40]. PSTi8 treatment reduces lipogenesis, enhances fatty acid oxidation, improves glucose homeostasis *via* increased glycogenesis and glycolysis, and decreases gluconeogenesis in streptozotocin-induced diabetic mice[35,38]. The insulin-sensitizing effect of PSTi8 is equivalent to that of metformin, one of the most commonly used oral antidiabetic agents. Therefore, its potential role as a new antidiabetic agent is an ongoing area of research[39].

***Catestatin***

CST is indirectly associated with diabetes and carbohydrate metabolism by its effects on hypertension, obesity, and metabolic syndrome, and its possible use as a future antihypertensive or antiobesity agent has been considered[41]. External administration of CST reduces the bodyweight of obese *CHGA* KO mice[42] and can normalize catecholamine levels and baroreceptor function[34] to a state similar to that of wild-type mice. The obesity-reducing effects of CST result from enhancement of leptin receptor signaling and inhibition of alpha2-adrenergic receptor signaling[43]. *CHGA* KO mice fed a high-fat diet have elevated insulin levels. Treatment with external CST normalizes the glucose metabolism of hepatocytes and improves the insulin sensitivity of the animals[44]. Obese children and adolescents have a significantly lower serum CST levels than those in healthy controls. In a cohort of obese children, those with any symptoms of metabolic syndrome or increased cardiovascular risk had the lowest serum CST levels[45].

**ROLES OF GRANINS IN DIABETES MELLITUS**

Diabetes mellitus is one of the most prevalent diseases in our time. Recent estimates of the prevalence range from 4% to 10%, and more than 460 million diabetes patients worldwide. Approximately 10% of diabetes patients have type 1 diabetes mellitus (T1DM); most of the remaining patients have T2DM[46]. The former has an autoimmune pathomechanism; the latter is a consequence of insulin resistance. Furthermore, T1DM develops mostly in younger people, while T2DM develops at later ages[47,48]. Although our knowledge on the pathomechanism of diabetes is very extensive, new relationships between diabetes and molecules involved in the development or subsequent progression of the disease is still a recent and popular area of research[49]. Examples of these recently described molecules include CgA, CgB, SgII, and secretogranin III (SgIII), the CgA cleavage peptide derivatives PST, WE-14, and small N-terminal fragments CgA10-19 and CgA43-52.

**Chromogranin A**

***CgA in T1DM***

The role of CgA in the development of T1DM has been demonstrated by the absence of T1DM in *CHGA* KO nonobese diabetic (NOD) mice, in contrast to wild-type NOD mice (a TIDM animal model system)[50]. Furthermore, insulitis, the inflammation of the pancreatic islets, occurred in only one-fifth of *CHGA* KO NOD mice, but did occur in all wild-type NOD mice. Insulitis was accompanied by significantly decreased numbers of infiltrating CD4+ and CD8+ T cells in *CHGA* KO NOD mice. It should be noted that it was not possible to investigate more accurately whether the absence of the entire CgA molecule or any of its cleavage products prevented the development of T1DM in the *CHGA* KO NOD mouse model.

CgA has been reported to be elevated in approximately 20% of patients with T1DM when examined many years after the onset of the disease[51]. An even greater prevalence of high CgA levels was found in another study[52]. A positive correlation has been found between serum CgA and glycated hemoglobin (HbA1C) levels, with a slight but steady elevation of CgA with the increased duration of T1DM, indicating that CgA does not only contribute to T1DM pathogenesis, but also to disease progression[51].

Blood CgA level is elevated in enterochromaffin-like (ECL) cell hyperplasia, autoimmune gastritis, and in gastrointestinal neuroendocrine tumors[53,54], which are more frequent in T1DM patients than in the healthy population[53,55]. A significant proportion of patients with a high CgA level have ECL cell hyperplasia[51,55]; hence early detection of these conditions is possible with regular serum CgA level measurements[51,56]. There is a possible connection between ECL cell hyperplasia and high HbA1C in T1DM patients with high CgA. It is known from animal experiments that 70%-90% of the circulating PST is produced by gastric ECL cells[57], and PST is actively involved in the regulation of glucose homeostasis[5]. The worsened metabolic status and high CgA levels may result from the hyperplasia of ECL cells, which can be further impaired by the appearance of more advanced clinical symptoms and comorbidities.

***CgA cleavage products in T1DM***

The CgA cleavage products WE-14 (CgA324-337)[7], CgA10-19, and CgA43-52[58] are newly discovered autoantigens involved in the pathogenesis of T1DM. Embryonic medullary thymic epithelial cells do not contain CgA mRNA, which may serve as a cause for the insufficient deletion of CgA-reactive T cells[7,59] and autoimmunity against CgA-producing pancreatic beta cells. Among the aforementioned peptide products, CgA10-19, and CgA43-52 induced CD8+ T cell proliferation and displayed increased cytotoxic activity in both human T1DM patients and NOD mice[58]. In contrast, WE-14 has been shown to have CD4+ T cell autoreactivity[7] that does not occur in other gastro-entero-pancreatic tissues, except for pancreatic beta cells[60]. WE-14 presumably interacts with the major histocompatibility complex (MHC) class II antigens outside of the normal peptide binding grooves of MHC molecules, as WE-14 lacks the N-terminal amino acids that easily bind to the MHC class II antigen-binding sites[7]. The above observation that the antigenicity of WE-14 occurs only in pancreatic islets is presumably depends on a difference in the proteolytic processing of CgA in beta cells[7].

The modification of WE-14 by enzyme tissue transglutaminase (TGase)[61,62] or *in vitro* N-terminal arginine-leucine-glycine-leucine amino acid addition[63] dramatically increases its antigenic activity. Covalent cross-linking[14] between the side chains of glutamine and lysine caused by TGase[64] treatment increases the antigenicity of WE-14[65]. Similar to animal models, newly diagnosed T1DM patients have also been shown to exhibit elevated WE-14 antigenicity[62]. Antigenicity can be further increased if the patient’s blood has been treated with TGase *in vitro*[62].

Hybrid insulin peptides (HIPs) are formed by the coupling of proinsulin and other peptides, are stored within the same secretory granules[66], and include a peptide called 2.5HIP, which is formed by a fusion of a C-peptide fragment and WE-14[67]. CD4+ T cell autoimmunity against 2.5HIP was demonstrated in NOD mice[66,67]. Peripheral NOD mouse-specific CgA-reactive T cells (BDC2.5) can bind 2.5HIP with up to 100 times higher affinity than WE-14 or CgA29-42 alone[68], and the number of these HIP-reactive T cells increases with disease progression[66,67]. Human HIP-reactive CD4+ T cells have also been identified[66]. The development of T1DM can be prevented for more than 2 mo by transferring preactivated BDC2.5 T cells and 2.5HIP nanoparticles into NOD mice, whereas the disease manifested in untreated mice within 10 d[69].

Treating young NOD mice with liposomes containing a CgA mimotope (amino acid chain: AHHPIWARMDA) and the immunomodulator calcitriol (1α,25-dihydroxyvitamin D3) can postpone the development of T1DM[70]. Furthermore, the adoptive transfer of CD4+ T cells from liposome-treated animals into NOD severe-combined-immunodeficiency mice also suppressed the development of the disease[70].

***CgA and its cleavage product PST in other forms of diabetes***

The few published data on the relationship between CgA and T2DM are somewhat controversial. Kogawa *et al*[71,72] reported that salivary and serum CgA were significantly higher in T2DM patients than in healthy controls and patients with higher CgA values had worse glycemic control (HbA1C ≥ 7.0%)[71]. Impaired salivary flow was correlated with increased serum and salivary CgA levels and was associated with two genetic variants of *CHGA* (rs9658635 and rs9658655)[72]. In contrast to those findings, another study found that an almost negligible portion of T2DM patients had serum CgA levels above the normal upper limit (> 98.1 ng/mL)[73], and no differences were found in the laboratory results and anamnestic data between the groups with normal or high serum CgA levels[73].

Postprandial serum PST levels are significantly higher in patients with prediabetes[74] or T2DM[75] compared with healthy controls, and are associated with consequent hyperglycemia[75], possibly because of the effect of PST on GSIS[75,76]. Fasting PST levels of the patients and controls did not differ[75]. Another study found that obese T2DM patients had significantly higher PST levels than obese and healthy nonobese control subjects, and that weight loss did not affect the differences in PST levels[77]. Serum PST is increased in patients with gestational diabetes, and positive correlations of PST, epinephrine, and norepinephrine levels have also been observed[78].

**CHROMOGRANIN B AND SECRETOGRANINS**

Even though a few hundred publications on CgB are available, very little is known about its relationship to diabetes. CgB has been reported to play a role in physiological insulin secretion[16-18] and its posttranslational changes[79], altered processing[80], and decreased serum values[81] that have been observed in human diabetes. The expression of *CHGB* in the pancreatic islets was lower in human T2DM patients compared with healthy subjects[79]. T2DM patients treated with intensive conservative insulin treatment had a significantly (approximately 20%) lower CgB level than T2DM patients treated with other regimens of antidiabetic drugs, or healthy controls. The serum CgB levels in T1DM were approximately 20% of the levels in control subjects, suggesting that pancreatic beta cells may produce a significant amount of circulating CgB. Furthermore, an assumption has been made that diabetes heavily affects CgB production. The autoimmune destruction of pancreatic beta cells in T1DM, and the more advanced state of the disease in T2DM, which is usually also associated with beta cell impairment, could cause the lower CgB levels. However, further studies are needed to test that hypothesis[81].

Diabetic retinopathy (DR), in which choroidal and retinal microvascular changes occur as complications of diabetes mellitus[82], can be characterized by an altered processing of granins in the vitreous[80]. Small peptide fragments of CgA, CgB, and SgII, which have been proposed to have anti-inflammatory properties, are rare in the vitreous of DR patients, but large fragments are rare in healthy subjects. Some authors have raised the possibility that the absence of small granin fragments may play a role in the pathogenesis of DR: Posttranslational processing of granins may be damaged because of some diabetes-specific reasons that ultimately lead to the impairment of the intraocular angiogenic balance, thus contributing to the neovascularization[80].

SgIII a recently discovered DR-associated ligand with pro-angiogenic activity and selective binding. Based on cellular and animal-model studies, the effects of SgIII are restricted to the pathological condition, suggesting that the antibody against SgIII might be useful as a selective, anti-angiogenic drug in DR[83]. The angiogenic effect of SgIII could have been blocked *via* inhibition of the mitogen-activated protein kinase and extracellular signal-regulated kinase signaling pathways[84]. Consistent with the findings of animal studies, SgIII has been found only in the vitreous in humans[85]. Increased SgIII levels been found in DR patients compared with retinopathy originating in patients without diabetess. Moreover, high lipid levels and a high body mass index, which are characteristic of T2DM[48] have been described as risk factors of DR[86], and have been associated with even higher SgIII levels[85].

**CONCLUSION**

Granin proteins are produced by various neuronal, neuroendocrine, and endocrine cell types of different organs throughout the body. They contribute intracellularly to the selective secretion of various peptides. A variety of extracellular functions of biologically active cleavage products have also emerged during their evolution. Recent studies have reported that CgA, CgB, SgII, SgIII, SgVII and some of the CgA cleavage products influence glucose homeostasis and different forms of diabetes mellitus. CgA and its peptide derivatives take part in the development and subsequent progression of T1DM, and also regulate glucose homeostasis. CgB and SgVII are prominent in physiological insulin secretion, and SgII and SgIII mainly contribute to DR. More data on the activity of granins is available for T1DM than for T2DM. The potential application of PSTi8, CST, and antibodies against SgIII as future medications further increases the importance of granins in diabetes. Although our understanding of granin proteins in relation to glucose homeostasis and diabetes mellitus, the most recent studies pose new challenges and raise more questions than they answer. To properly answer these questions, further clinical and experimental studies are needed.

**ACKNOWLEDGEMENTS**

We are grateful to Mark Eyre for English proofreading.

**REFERENCES**

1 **Bartolomucci A**, Possenti R, Mahata SK, Fischer-Colbrie R, Loh YP, Salton SR. The extended granin family: structure, function, and biomedical implications. *Endocr Rev* 2011; **32**: 755-797 [PMID: 21862681 DOI: 10.1210/er.2010-0027]

2 **Feldman SA**, Eiden LE. The chromogranins: their roles in secretion from neuroendocrine cells and as markers for neuroendocrine neoplasia. *Endocr Pathol* 2003; **14**: 3-23 [PMID: 12746559 DOI: 10.1385/ep:14:1:3]

3 **Helle KB**, Metz-Boutigue MH, Cerra MC, Angelone T. Chromogranins: from discovery to current times. *Pflugers Arch* 2018; **470**: 143-154 [PMID: 28875377 DOI: 10.1007/s00424-017-2027-6]

4 **Simon JP**, Aunis D. Biochemistry of the chromogranin A protein family. *Biochem J* 1989; **262**: 1-13 [PMID: 2684154 DOI: 10.1042/bj2620001]

5 **Sánchez-Margalet V**, González-Yanes C, Najib S, Santos-Alvarez J. Metabolic effects and mechanism of action of the chromogranin A-derived peptide pancreastatin. *Regul Pept* 2010; **161**: 8-14 [PMID: 20184923 DOI: 10.1016/j.regpep.2010.02.005]

6 **Strub JM**, Goumon Y, Lugardon K, Capon C, Lopez M, Moniatte M, Van Dorsselaer A, Aunis D, Metz-Boutigue MH. Antibacterial activity of glycosylated and phosphorylated chromogranin A-derived peptide 173-194 from bovine adrenal medullary chromaffin granules. *J Biol Chem* 1996; **271**: 28533-28540 [PMID: 8910482 DOI: 10.1074/jbc.271.45.28533]

7 **Stadinski BD**, Delong T, Reisdorph N, Reisdorph R, Powell RL, Armstrong M, Piganelli JD, Barbour G, Bradley B, Crawford F, Marrack P, Mahata SK, Kappler JW, Haskins K. Chromogranin A is an autoantigen in type 1 diabetes. *Nat Immunol* 2010; **11**: 225-231 [PMID: 20139986 DOI: 10.1038/ni.1844]

8 **Fischer-Colbrie R**, Eder S, Lovisetti-Scamihorn P, Becker A, Laslop A. Neuroendocrine secretory protein 55: a novel marker for the constitutive secretory pathway. *Ann N Y Acad Sci* 2002; **971**: 317-322 [PMID: 12438142 DOI: 10.1111/j.1749-6632.2002.tb04486.x]

9 **Fischer-Colbrie R**, Laslop A, Kirchmair R. Secretogranin II: molecular properties, regulation of biosynthesis and processing to the neuropeptide secretoneurin. *Prog Neurobiol* 1995; **46**: 49-70 [PMID: 7568909 DOI: 10.1016/0301-0082(94)00060-u]

10 **Hendy GN**, Bevan S, Mattei MG, Mouland AJ. Chromogranin A. *Clin Invest Med* 1995; **18**: 47-65 [PMID: 7768066]

11 **Winkler H**, Fischer-Colbrie R. The chromogranins A and B: the first 25 years and future perspectives. *Neuroscience* 1992; **49**: 497-528 [PMID: 1501763 DOI: 10.1016/0306-4522(92)90222-n]

12 **Li W**, Webster KA, LeBlanc ME, Tian H. Secretogranin III: a diabetic retinopathy-selective angiogenic factor. *Cell Mol Life Sci* 2018; **75**: 635-647 [PMID: 28856381 DOI: 10.1007/s00018-017-2635-5]

13 **Mbikay M**, Seidah NG, Chrétien M. Neuroendocrine secretory protein 7B2: structure, expression and functions. *Biochem J* 2001; **357**: 329-342 [PMID: 11439082 DOI: 10.1042/0264-6021:3570329]

14 **Herold Z**, Doleschall M, Kovesdi A, Patocs A, Somogyi A. Chromogranin A and its role in the pathogenesis of diabetes mellitus. *Endokrynol Pol* 2018; **69**: 598-610 [PMID: 30074235 DOI: 10.5603/EP.a2018.0052]

15 **Wollam J**, Mahata S, Riopel M, Hernandez-Carretero A, Biswas A, Bandyopadhyay GK, Chi NW, Eiden LE, Mahapatra NR, Corti A, Webster NJG, Mahata SK. Chromogranin A regulates vesicle storage and mitochondrial dynamics to influence insulin secretion. *Cell Tissue Res* 2017; **368**: 487-501 [PMID: 28220294 DOI: 10.1007/s00441-017-2580-5]

16 **Bearrows SC**, Bauchle CJ, Becker M, Haldeman JM, Swaminathan S, Stephens SB. Chromogranin B regulates early-stage insulin granule trafficking from the Golgi in pancreatic islet β-cells. *J Cell Sci* 2019; **132** [PMID: 31182646 DOI: 10.1242/jcs.231373]

17 **Giordano T**, Brigatti C, Podini P, Bonifacio E, Meldolesi J, Malosio ML. Beta cell chromogranin B is partially segregated in distinct granules and can be released separately from insulin in response to stimulation. *Diabetologia* 2008; **51**: 997-1007 [PMID: 18437352 DOI: 10.1007/s00125-008-0980-5]

18 **Obermüller S**, Calegari F, King A, Lindqvist A, Lundquist I, Salehi A, Francolini M, Rosa P, Rorsman P, Huttner WB, Barg S. Defective secretion of islet hormones in chromogranin-B deficient mice. *PLoS One* 2010; **5**: e8936 [PMID: 20126668 DOI: 10.1371/journal.pone.0008936]

19 **Cocco C**, Brancia C, Pirisi I, D'Amato F, Noli B, Possenti R, Ferri GL. VGF metabolic-related gene: distribution of its derived peptides in mammalian pancreatic islets. *J Histochem Cytochem* 2007; **55**: 619-628 [PMID: 17312015 DOI: 10.1369/jhc.6A7040.2007]

20 **Stephens SB**, Edwards RJ, Sadahiro M, Lin WJ, Jiang C, Salton SR, Newgard CB. The Prohormone VGF Regulates β Cell Function *via* Insulin Secretory Granule Biogenesis. *Cell Rep* 2017; **20**: 2480-2489 [PMID: 28877479 DOI: 10.1016/j.celrep.2017.08.050]

21 **Schmid GM**, Meda P, Caille D, Wargent E, O'Dowd J, Hochstrasser DF, Cawthorne MA, Sanchez JC. Inhibition of insulin secretion by betagranin, an N-terminal chromogranin A fragment. *J Biol Chem* 2007; **282**: 12717-12724 [PMID: 17289672 DOI: 10.1074/jbc.M700788200]

22 **Cetin Y**, Aunis D, Bader MF, Galindo E, Jörns A, Bargsten G, Grube D. Chromostatin, a chromogranin A-derived bioactive peptide, is present in human pancreatic insulin (beta) cells. *Proc Natl Acad Sci U S A* 1993; **90**: 2360-2364 [PMID: 8096340 DOI: 10.1073/pnas.90.6.2360]

23 **Karlsson E**, Stridsberg M, Sandler S. Chromogranin-B regulation of IAPP and insulin secretion. *Regul Pept* 2000; **87**: 33-39 [PMID: 10710286 DOI: 10.1016/s0167-0115(99)00105-6]

24 **González-Yanes C**, Sánchez-Margalet V. Pancreastatin, a chromogranin A-derived peptide, inhibits leptin and enhances UCP-2 expression in isolated rat adipocytes. *Cell Mol Life Sci* 2003; **60**: 2749-2756 [PMID: 14685697 DOI: 10.1007/s00018-003-3346-7]

25 **Sánchez V**, Lucas M, Calvo JR, Goberna R. Glycogenolytic effect of pancreastatin in isolated rat hepatocytes is mediated by a cyclic-AMP-independent Ca(2+)-dependent mechanism. *Biochem J* 1992; **284 ( Pt 3)**: 659-662 [PMID: 1377910 DOI: 10.1042/bj2840659]

26 **Schmidt WE**, Creutzfeldt W. Pancreastatin--a novel regulatory peptide? *Acta Oncol* 1991; **30**: 441-449 [PMID: 1854501 DOI: 10.3109/02841869109092399]

27 **Tatemoto K**, Efendić S, Mutt V, Makk G, Feistner GJ, Barchas JD. Pancreastatin, a novel pancreatic peptide that inhibits insulin secretion. *Nature* 1986; **324**: 476-478 [PMID: 3537810 DOI: 10.1038/324476a0]

28 **Ahrén B**, Bertrand G, Roye M, Ribes G. Pancreastatin modulates glucose-stimulated insulin secretion from the perfused rat pancreas. *Acta Physiol Scand* 1996; **158**: 63-70 [PMID: 8876749 DOI: 10.1046/j.1365-201X.1996.525291000.x]

29 **Sanchez V**, Calvo JR, Goberna R. Glycogenolytic effect of pancreastatin in the rat. *Biosci Rep* 1990; **10**: 87-91 [PMID: 2187544 DOI: 10.1007/BF01116856]

30 **Valicherla GR**, Hossain Z, Mahata SK, Gayen JR. Pancreastatin is an endogenous peptide that regulates glucose homeostasis. *Physiol Genomics* 2013; **45**: 1060-1071 [PMID: 24064537 DOI: 10.1152/physiolgenomics.00131.2013]

31 **Sánchez-Margalet V**, González-Yanes C, Najib S. Pancreastatin, a chromogranin A-derived peptide, inhibits DNA and protein synthesis by producing nitric oxide in HTC rat hepatoma cells. *J Hepatol* 2001; **35**: 80-85 [PMID: 11495046 DOI: 10.1016/s0168-8278(01)00071-x]

32 **Gayen JR**, Saberi M, Schenk S, Biswas N, Vaingankar SM, Cheung WW, Najjar SM, O'Connor DT, Bandyopadhyay G, Mahata SK. A novel pathway of insulin sensitivity in chromogranin A null mice: a crucial role for pancreastatin in glucose homeostasis. *J Biol Chem* 2009; **284**: 28498-28509 [PMID: 19706599 DOI: 10.1074/jbc.M109.020636]

33 **Mosén H**, Salehi A, Henningsson R, Lundquist I. Nitric oxide inhibits, and carbon monoxide activates, islet acid alpha-glucoside hydrolase activities in parallel with glucose-stimulated insulin secretion. *J Endocrinol* 2006; **190**: 681-693 [PMID: 17003269 DOI: 10.1677/joe.1.06890]

34 **Gayen JR**, Gu Y, O'Connor DT, Mahata SK. Global disturbances in autonomic function yield cardiovascular instability and hypertension in the chromogranin a null mouse. *Endocrinology* 2009; **150**: 5027-5035 [PMID: 19819970 DOI: 10.1210/en.2009-0429]

35 **Gupta AP**, Garg R, Singh P, Goand UK, Syed AA, Valicherla GR, Riyazuddin M, Mugale MN, Gayen JR. Pancreastatin inhibitor PSTi8 protects the obesity associated skeletal muscle insulin resistance in diet induced streptozotocin-treated diabetic mice. *Eur J Pharmacol* 2020; **881**: 173204 [PMID: 32439261 DOI: 10.1016/j.ejphar.2020.173204]

36 **Gupta AP**, Syed AA, Garg R, Goand UK, Singh P, Riyazuddin M, Valicherla GR, Husain A, Gayen JR. Pancreastatin inhibitor PSTi8 attenuates hyperinsulinemia induced obesity and inflammation mediated insulin resistance *via* MAPK/NOX3-JNK pathway. *Eur J Pharmacol* 2019; **864**: 172723 [PMID: 31586632 DOI: 10.1016/j.ejphar.2019.172723]

37 **Hossain Z**, Valicherla GR, Gupta AP, Syed AA, Riyazuddin M, Chandra S, Siddiqi MI, Gayen JR. 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 [PMID: 29880906 DOI: 10.1038/s41598-018-27018-8]

38 **Valicherla GR**, Gupta AP, Hossain Z, Riyazuddin M, Syed AA, Husain A, Lahiri S, Dave KM, Gayen JR. Pancreastatin inhibitor, PSTi8 ameliorates metabolic health by modulating AKT/GSK-3β and PKCλ/ζ/SREBP1c pathways in high fat diet induced insulin resistance in peri-/post-menopausal rats. *Peptides* 2019; **120**: 170147 [PMID: 31473204 DOI: 10.1016/j.peptides.2019.170147]

39 **Valicherla GR**, Riyazuddin M, Shahi S, Gupta AP, Syed AA, Husain A, Gayen JR. LC-ESI-MS/MS assay development and validation of a novel antidiabetic peptide PSTi8 in mice plasma using SPE: An application to pharmacokinetics. *J Pharm Biomed Anal* 2020; **180**: 113074 [PMID: 31891874 DOI: 10.1016/j.jpba.2019.113074]

40 **Gupta AP**, Singh P, Garg R, Valicherla GR, Riyazuddin M, Syed AA, Hossain Z, Gayen JR. Pancreastatin inhibitor activates AMPK pathway *via* GRP78 and ameliorates dexamethasone induced fatty liver disease in C57BL/6 mice. *Biomed Pharmacother* 2019; **116**: 108959 [PMID: 31108350 DOI: 10.1016/j.biopha.2019.108959]

41 **Bandyopadhyay GK**, Mahata SK. Chromogranin A Regulation of Obesity and Peripheral Insulin Sensitivity. *Front Endocrinol (Lausanne)* 2017; **8**: 20 [PMID: 28228748 DOI: 10.3389/fendo.2017.00020]

42 **Mahapatra NR**, O'Connor DT, Vaingankar SM, Hikim AP, Mahata M, Ray S, Staite E, Wu H, Gu Y, Dalton N, Kennedy BP, Ziegler MG, Ross J, Mahata SK. Hypertension from targeted ablation of chromogranin A can be rescued by the human ortholog. *J Clin Invest* 2005; **115**: 1942-1952 [PMID: 16007257 DOI: 10.1172/JCI24354]

43 **Kim SJ**, Tang T, Abbott M, Viscarra JA, Wang Y, Sul HS. AMPK Phosphorylates Desnutrin/ATGL and Hormone-Sensitive Lipase To Regulate Lipolysis and Fatty Acid Oxidation within Adipose Tissue. *Mol Cell Biol* 2016; **36**: 1961-1976 [PMID: 27185873 DOI: 10.1128/MCB.00244-16]

44 **Ying W**, Mahata S, Bandyopadhyay GK, Zhou Z, Wollam J, Vu J, Mayoral R, Chi NW, Webster NJG, Corti A, Mahata SK. Catestatin Inhibits Obesity-Induced Macrophage Infiltration and Inflammation in the Liver and Suppresses Hepatic Glucose Production, Leading to Improved Insulin Sensitivity. *Diabetes* 2018; **67**: 841-848 [PMID: 29432123 DOI: 10.2337/db17-0788]

45 **Simunovic M**, Supe-Domic D, Karin Z, Degoricija M, Paradzik M, Bozic J, Unic I, Skrabic V. Serum catestatin concentrations are decreased in obese children and adolescents. *Pediatr Diabetes* 2019; **20**: 549-555 [PMID: 30714297 DOI: 10.1111/pedi.12825]

46 **International Diabetes Federation.** IDF Diabetes Atlas. 9th ed. Brussels: International Diabetes Federation, 2019. [cited 4 January 2021]. Available from: https://diabetesatlas.org/en/

47 **Katsarou A**, Gudbjörnsdottir S, Rawshani A, Dabelea D, Bonifacio E, Anderson BJ, Jacobsen LM, Schatz DA, Lernmark Å. Type 1 diabetes mellitus. *Nat Rev Dis Primers* 2017; **3**: 17016 [PMID: 28358037 DOI: 10.1038/nrdp.2017.16]

48 **DeFronzo RA**, Ferrannini E, Groop L, Henry RR, Herman WH, Holst JJ, Hu FB, Kahn CR, Raz I, Shulman GI, Simonson DC, Testa MA, Weiss R. Type 2 diabetes mellitus. *Nat Rev Dis Primers* 2015; **1**: 15019 [PMID: 27189025 DOI: 10.1038/nrdp.2015.19]

49 **Broedbaek K**, Hilsted L. Chromogranin A as biomarker in diabetes. *Biomark Med* 2016; **10**: 1181-1189 [PMID: 27611656 DOI: 10.2217/bmm-2016-0091]

50 **Baker RL**, Bradley B, Wiles TA, Lindsay RS, Barbour G, Delong T, Friedman RS, Haskins K. Cutting Edge: Nonobese Diabetic Mice Deficient in Chromogranin A Are Protected from Autoimmune Diabetes. *J Immunol* 2016; **196**: 39-43 [PMID: 26608914 DOI: 10.4049/jimmunol.1501190]

51 **Herold Z**, Herold M, Nagy P, Patocs A, Doleschall M, Somogyi A. Serum chromogranin A level continuously rises with the progression of type 1 diabetes, and indicates the presence of both enterochromaffin-like cell hyperplasia and autoimmune gastritis. *J Diabetes Investig* 2020; **11**: 865-873 [PMID: 31883432 DOI: 10.1111/jdi.13203]

52 **Ebert A**, König J, Frommer L, Schuppan D, Kahaly GJ. Chromogranin Serves as Novel Biomarker of Endocrine and Gastric Autoimmunity. *J Clin Endocrinol Metab* 2020; **105** [PMID: 32436949 DOI: 10.1210/clinem/dgaa288]

53 **De Block CE**, De Leeuw IH, Van Gaal LF. Autoimmune gastritis in type 1 diabetes: a clinically oriented review. *J Clin Endocrinol Metab* 2008; **93**: 363-371 [PMID: 18029461 DOI: 10.1210/jc.2007-2134]

54 **Vinik AI**, Silva MP, Woltering EA, Go VL, Warner R, Caplin M. Biochemical testing for neuroendocrine tumors. *Pancreas* 2009; **38**: 876-889 [PMID: 19855234 DOI: 10.1097/MPA.0b013e3181bc0e77]

55 **De Block CE**, Colpin G, Thielemans K, Coopmans W, Bogers JJ, Pelckmans PA, Van Marck EA, Van Hoof V, Martin M, De Leeuw IH, Bouillon R, Van Gaal LF. Neuroendocrine tumor markers and enterochromaffin-like cell hyper/dysplasia in type 1 diabetes. *Diabetes Care* 2004; **27**: 1387-1393 [PMID: 15161793 DOI: 10.2337/diacare.27.6.1387]

56 **Herold Z**, Uhlyarik A, Herold M, Nagy P, Huszty GD, Rosta K, Doleschall M, Somogyi A. Regular chromogranin A monitoring facilitated the early detection of a gastrointestinal neuroendocrine tumour in a patient with type 1 diabetes. *Endokrynol Pol* 2020; **71**: 483-484 [PMID: 32856287 DOI: 10.5603/EP.a2020.0054]

57 **Kimura K**, Chen D, Lindström E, Zhao CM, Håkanson R. Evidence that rat stomach ECL cells represent the main source of circulating pancreastatin. *Regul Pept* 1997; **68**: 177-180 [PMID: 9100284 DOI: 10.1016/s0167-0115(96)02117-9]

58 **Li Y**, Zhou L, Li Y, Zhang J, Guo B, Meng G, Chen X, Zheng Q, Zhang L, Zhang M, Wang L. 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 [PMID: 25958206 DOI: 10.1016/j.clim.2015.04.017]

59 **Anderson MS**, Venanzi ES, Klein L, Chen Z, Berzins SP, Turley SJ, von Boehmer H, Bronson R, Dierich A, Benoist C, Mathis D. Projection of an immunological self shadow within the thymus by the aire protein. *Science* 2002; **298**: 1395-1401 [PMID: 12376594 DOI: 10.1126/science.1075958]

60 **Gleeson CM**, Curry WJ, Johnston CF, Buchanan KD. Occurrence of WE-14 and chromogranin A-derived peptides in tissues of the human and bovine gastro-entero-pancreatic system and in human neuroendocrine neoplasia. *J Endocrinol* 1996; **151**: 409-420 [PMID: 8994386 DOI: 10.1677/joe.0.1510409]

61 **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**: 3239-3246 [PMID: 22912420 DOI: 10.2337/db12-0112]

62 **Gottlieb PA**, Delong T, Baker RL, Fitzgerald-Miller L, Wagner R, Cook G, Rewers MR, Michels A, Haskins K. Chromogranin A is a T cell antigen in human type 1 diabetes. *J Autoimmun* 2014; **50**: 38-41 [PMID: 24239002 DOI: 10.1016/j.jaut.2013.10.003]

63 **Jin N**, Wang Y, Crawford F, White J, Marrack P, Dai S, Kappler JW. N-terminal additions to the WE14 peptide of chromogranin A create strong autoantigen agonists in type 1 diabetes. *Proc Natl Acad Sci U S A* 2015; **112**: 13318-13323 [PMID: 26453556 DOI: 10.1073/pnas.1517862112]

64 **Sollid LM**. Molecular basis of celiac disease. *Annu Rev Immunol* 2000; **18**: 53-81 [PMID: 10837052 DOI: 10.1146/annurev.immunol.18.1.53]

65 **Guillemot J**, Guérin M, Thouënnon E, Montéro-Hadjadje M, Leprince J, Lefebvre H, Klein M, Muresan M, Anouar Y, Yon L. Characterization and plasma measurement of the WE-14 peptide in patients with pheochromocytoma. *PLoS One* 2014; **9**: e88698 [PMID: 24523932 DOI: 10.1371/journal.pone.0088698]

66 **Delong T**, Wiles TA, Baker RL, Bradley B, Barbour G, Reisdorph R, Armstrong M, Powell RL, Reisdorph N, Kumar N, Elso CM, DeNicola M, Bottino R, Powers AC, Harlan DM, Kent SC, Mannering SI, Haskins K. Pathogenic CD4 T cells in type 1 diabetes recognize epitopes formed by peptide fusion. *Science* 2016; **351**: 711-714 [PMID: 26912858 DOI: 10.1126/science.aad2791]

67 **Baker RL**, Jamison BL, Wiles TA, Lindsay RS, Barbour G, Bradley B, Delong T, Friedman RS, Nakayama M, Haskins K. CD4 T Cells Reactive to Hybrid Insulin Peptides Are Indicators of Disease Activity in the NOD Mouse. *Diabetes* 2018; **67**: 1836-1846 [PMID: 29976617 DOI: 10.2337/db18-0200]

68 **Liu B**, Hood JD, Kolawole EM, Woodruff DM, Vignali DA, Bettini M, Evavold BD. A Hybrid Insulin Epitope Maintains High 2D Affinity for Diabetogenic T Cells in the Periphery. *Diabetes* 2020; **69**: 381-391 [PMID: 31806623 DOI: 10.2337/db19-0399]

69 **Jamison BL**, Neef T, Goodspeed A, Bradley B, Baker RL, Miller SD, Haskins K. Nanoparticles Containing an Insulin-ChgA Hybrid Peptide Protect from Transfer of Autoimmune Diabetes by Shifting the Balance between Effector T Cells and Regulatory T Cells. *J Immunol* 2019; **203**: 48-57 [PMID: 31109955 DOI: 10.4049/jimmunol.1900127]

70 **Bergot AS**, Buckle I, Cikaluru S, Naranjo JL, Wright CM, Zheng G, Talekar M, Hamilton-Williams EE, Thomas R. Regulatory T Cells Induced by Single-Peptide Liposome Immunotherapy Suppress Islet-Specific T Cell Responses to Multiple Antigens and Protect from Autoimmune Diabetes. *J Immunol* 2020; **204**: 1787-1797 [PMID: 32111734 DOI: 10.4049/jimmunol.1901128]

71 **Kogawa EM**, Grisi DC, Falcão DP, Amorim IA, Rezende TM, da Silva IC, Silva ON, Franco OL, de Amorim RF. Impact of glycemic control on oral health status in type 2 diabetes individuals and its association with salivary and plasma levels of chromogranin A. *Arch Oral Biol* 2016; **62**: 10-19 [PMID: 26605682 DOI: 10.1016/j.archoralbio.2015.11.005]

72 **Kogawa EM**, Grisi DC, Falcão DP, Amorim IA, Rezende TM, da Silva IC, Silva ON, Franco OL, de Amorim RF. Salivary function impairment in type 2 Diabetes patients associated with concentration and genetic polymorphisms of chromogranin A. *Clin Oral Investig* 2016; **20**: 2083-2095 [PMID: 26750135 DOI: 10.1007/s00784-015-1705-z]

73 **Herold Z**, Herold M, Doleschall M, Somogyi A. [Serum chromogranin A level in type 2 diabetes patients]. *Diabetol Hung* 2020; **28**:91-96 [DOI: 10.24121/dh.2020.9]

74 **Sánchez-Margalet V**, Valle M, Lobón JA, Maldonado A, Escobar-Jimenez F, Oliván J, Pérez-Cano R, Goberna R. Increased plasma pancreastatin-like immunoreactivity levels in non-obese patients with essential hypertension. *J Hypertens* 1995; **13**: 251-258 [PMID: 7615956]

75 **Tateishi K**, Funakoshi A, Wakasugi H, Iguchi H, Shinozaki H, Abe M, Funakoshi S, Tamamura H, Yajima H, Matsuoka Y. Plasma pancreastatin-like immunoreactivity in various diseases. *J Clin Endocrinol Metab* 1989; **69**: 1305-1308 [PMID: 2555388 DOI: 10.1210/jcem-69-6-1305]

76 **Funakoshi A**, Tateishi K, Shinozaki H, Matsumoto M, Wakasugi H. Elevated plasma levels of pancreastatin (PST) in patients with non-insulin-dependent diabetes mellitus (NIDDM). *Regul Pept* 1990; **30**: 159-164 [PMID: 2274680 DOI: 10.1016/0167-0115(90)90056-3]

77 **O'Connor DT**, Cadman PE, Smiley C, Salem RM, Rao F, Smith J, Funk SD, Mahata SK, Mahata M, Wen G, Taupenot L, Gonzalez-Yanes C, Harper KL, Henry RR, Sanchez-Margalet V. Pancreastatin: multiple actions on human intermediary metabolism in vivo, variation in disease, and naturally occurring functional genetic polymorphism. *J Clin Endocrinol Metab* 2005; **90**: 5414-5425 [PMID: 15956083 DOI: 10.1210/jc.2005-0408]

78 **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**: 1951-1954 [PMID: 9802749 DOI: 10.2337/diacare.21.11.1951]

79 **Bugliani M**, Liechti R, Cheon H, Suleiman M, Marselli L, Kirkpatrick C, Filipponi F, Boggi U, Xenarios I, Syed F, Ladriere L, Wollheim C, Lee MS, Marchetti P. Microarray analysis of isolated human islet transcriptome in type 2 diabetes and the role of the ubiquitin-proteasome system in pancreatic beta cell dysfunction. *Mol Cell Endocrinol* 2013; **367**: 1-10 [PMID: 23246353 DOI: 10.1016/j.mce.2012.12.001]

80 **Fournier I**, Gaucher D, Chich JF, Bach C, Shooshtarizadeh P, Picaud S, Bourcier T, Speeg-Schatz C, Strub JM, Van Dorsselaer A, Corti A, Aunis D, Metz-Boutigue MH. Processing of chromogranins/secretogranin in patients with diabetic retinopathy. *Regul Pept* 2011; **167**: 118-124 [PMID: 21185877 DOI: 10.1016/j.regpep.2010.12.004]

81 **Herold Z**, Herold M, Rosta K, Doleschall M, Somogyi A. Lower serum chromogranin B level is associated with type 1 diabetes and with type 2 diabetes patients with intensive conservative insulin treatment. *Diabetol Metab Syndr* 2020; **12**: 61 [PMID: 32684986 DOI: 10.1186/s13098-020-00569-5]

82 **Duh EJ**, Sun JK, Stitt AW. Diabetic retinopathy: current understanding, mechanisms, and treatment strategies. *JCI Insight* 2017; **2** [PMID: 28724805 DOI: 10.1172/jci.insight.93751]

83 **LeBlanc ME**, Wang W, Chen X, Caberoy NB, Guo F, Shen C, Ji Y, Tian H, Wang H, Chen R, Li W. Secretogranin III as a disease-associated ligand for antiangiogenic therapy of diabetic retinopathy. *J Exp Med* 2017; **214**: 1029-1047 [PMID: 28330905 DOI: 10.1084/jem.20161802]

84 **Tang F**, Pacheco MTF, Chen P, Liang D, Li W. Secretogranin III promotes angiogenesis through MEK/ERK signaling pathway. *Biochem Biophys Res Commun* 2018; **495**: 781-786 [PMID: 29154827 DOI: 10.1016/j.bbrc.2017.11.080]

85 **Jiao MF**, Sun S, Wang MM, Dong LJ, Hu BJ, Liu JP, Li W, Li XR. [The observation of secretogranin Ⅲ in the peripheral blood and vitreous of patients with diabetic retinopathy]. *Zhonghua Yan Ke Za Zhi* 2020; **56**: 933-937 [PMID: 33342120 DOI: 10.3760/cma.j.cn112142-20200410-00260]

86 **van Leiden HA**, Dekker JM, Moll AC, Nijpels G, Heine RJ, Bouter LM, Stehouwer CD, Polak BC. Blood pressure, lipids, and obesity are associated with retinopathy: the hoorn study. *Diabetes Care* 2002; **25**: 1320-1325 [PMID: 12145228 DOI: 10.2337/diacare.25.8.1320]

87 **Neuhold N**, Ullrich R. Secretogranin IV immunoreactivity in medullary thyroid carcinoma: an immunohistochemical study of 62 cases. *Virchows Arch A Pathol Anat Histopathol* 1993; **423**: 85-89 [PMID: 7692664 DOI: 10.1007/BF01606581]

88 **Ischia R**, Lovisetti-Scamihorn P, Hogue-Angeletti R, Wolkersdorfer M, Winkler H, Fischer-Colbrie R. Molecular cloning and characterization of NESP55, a novel chromogranin-like precursor of a peptide with 5-HT1B receptor antagonist activity. *J Biol Chem* 1997; **272**: 11657-11662 [PMID: 9111083 DOI: 10.1074/jbc.272.17.11657]

89 **Bresciani E**, Possenti R, Coco S, Rizzi L, Meanti R, Molteni L, Locatelli V, Torsello A. TLQP-21, A VGF-Derived Peptide Endowed of Endocrine and Extraendocrine Properties: Focus on In Vitro Calcium Signaling. *Int J Mol Sci* 2019; **21** [PMID: 31878142 DOI: 10.3390/ijms21010130]

90 **Wardman JH**, Berezniuk I, Di S, Tasker JG, Fricker LD. ProSAAS-derived peptides are colocalized with neuropeptide Y and function as neuropeptides in the regulation of food intake. *PLoS One* 2011; **6**: e28152 [PMID: 22164236 DOI: 10.1371/journal.pone.0028152]

**Footnotes**

**Conflict-of-interest statement:** The authors have no conflicts of interest to declare.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Manuscript source:** Invited manuscript

**Peer-review started:** January 27, 2021

**First decision:** February 25, 2021

**Article in press:**

**Specialty type:** Endocrinology and metabolism

**Country/Territory of origin:** Hungary

**Peer-review report’s scientific quality classification**

Grade A (Excellent): A

Grade B (Very good): B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Liu D **S-Editor:** Fan JR **L-Editor:** Filipodia **P-Editor:**

**Table 1 Names, loci, and molecular masses of granin proteins[1,2]**

|  |  |  |  |
| --- | --- | --- | --- |
| **Name** | **Synonym** | **Locus** | **Number of amino acids and calculated molecular mass (kDa)** |
| Chromogranin A | Parathyroid secretory protein 1 | 14q32.12 | 439 (49 kDa) |
| Chromogranin B | Secretogranin I | 20pter-p12 | 657 (77 kDa) |
| Secretogranin II | Chromogranin C | 2q35-q36 | 587 (68 kDa) |
| Secretogranin III | – | 15q21 | 449 (51 kDa) |
| HISL-191 | Secretogranin IV | *–* | *–* |
| 7B2 | Secretogranin V | 15q13-q14 | 186 (21 kDa) |
| NESP55 | Secretogranin VI | 20q13.2 | 201 (23 kDa) |
| VGF | Secretogranin VII | 7q22.1 | 593 (65 kDa) |
| proSAAS | Secretogranin VIII | Xp11.23 | 227 (24 kDa) |

1HISL-19 has only been confirmed with monoclonal antibodies; *in vivo* isolation has not been successful to date[2,87]. NESP55: Neuroendocrine secretory protein with an apparent molecular weight of 55,000 Daltons.

**Table 2 Cleavage products of granin proteins[1,3,88-90]**

|  |  |
| --- | --- |
| **Granin protein** | **Cleavage product** |
| CgA1 | Vasostatin-I (CgA1-76) and -II (CgA1-115)  Betagranin (CgA1-128)  CgA10-19 and CgA43-521  Chromofungin (CgA47-66)  Vasoconstriction-inhibiting factor (CgA79-113)  Chromostatin (CgA124-143)  Chromacin (CgA173-194)  Pancreastatin (CgA250-301)1  WE-14 (CgA324-337)1  Cateslitin (CgA344-358)  Catestatin (CgA352-372)1  Parastatin (CgA357-428)  GE-25 (CgA367-391)  Serpinin (CgA417-442) |
| CgB1 | CgB1-41  GAWK (CgB420-493)  BAM-1745 (CgB579-593)  PE-11 (CgB555-565)  Secretolytin (CgB647-657)  43kDa large CgB fragment |
| SgII1 | Secretoneurin (conjugate of SgII133-151 and SgII154-186)  EM66 (66 amino acid long)  Manserin (SgII497-536) |
| SgIII1 | –2 |
| HISL-19 | –2 |
| 7B2 | –2 |
| NESP55 | LSAL (NESP55159-162)  GAIPIRRH (NESP55234-241) |
| VGF | Neuroendocrine regulatory peptide-1 (VGF281-306)  Neuroendocrine regulatory peptide-2 (VGF310-347)  NAPP129 or VGF20 (VGF417-617)  TPGH (VGF422-430)  TLQP-21 (VGF556-576)  TLQP-62 or VGF10 (VGF556-617)  HHPD-41 (VGF576-617)  AQEE-11 (VGF588-599)  AQEE-30 (VGF588-617)  LQEQ-19 (VGF599-617) |
| proSAAS | KEP (proSAAS1-7)  Big SAAS (proSAAS1-26)  Little SAAS (proSAAS9-26)  GAV  PEN (proSAAS188-209)  PEN-LEN (proSAAS188-227)  Little LEN (proSAAS212-221)  Big LEN (proSAAS212-227) |

1Granins and their cleavage products involved in carbohydrate metabolism; 2No cleavage product described to date. CgA: Chromogranin A; CgB: Chromogranin B; NESP55: Neuroendocrine secretory protein with an apparent molecular weight of 55000 Daltons; SgII: Secretogranin II.