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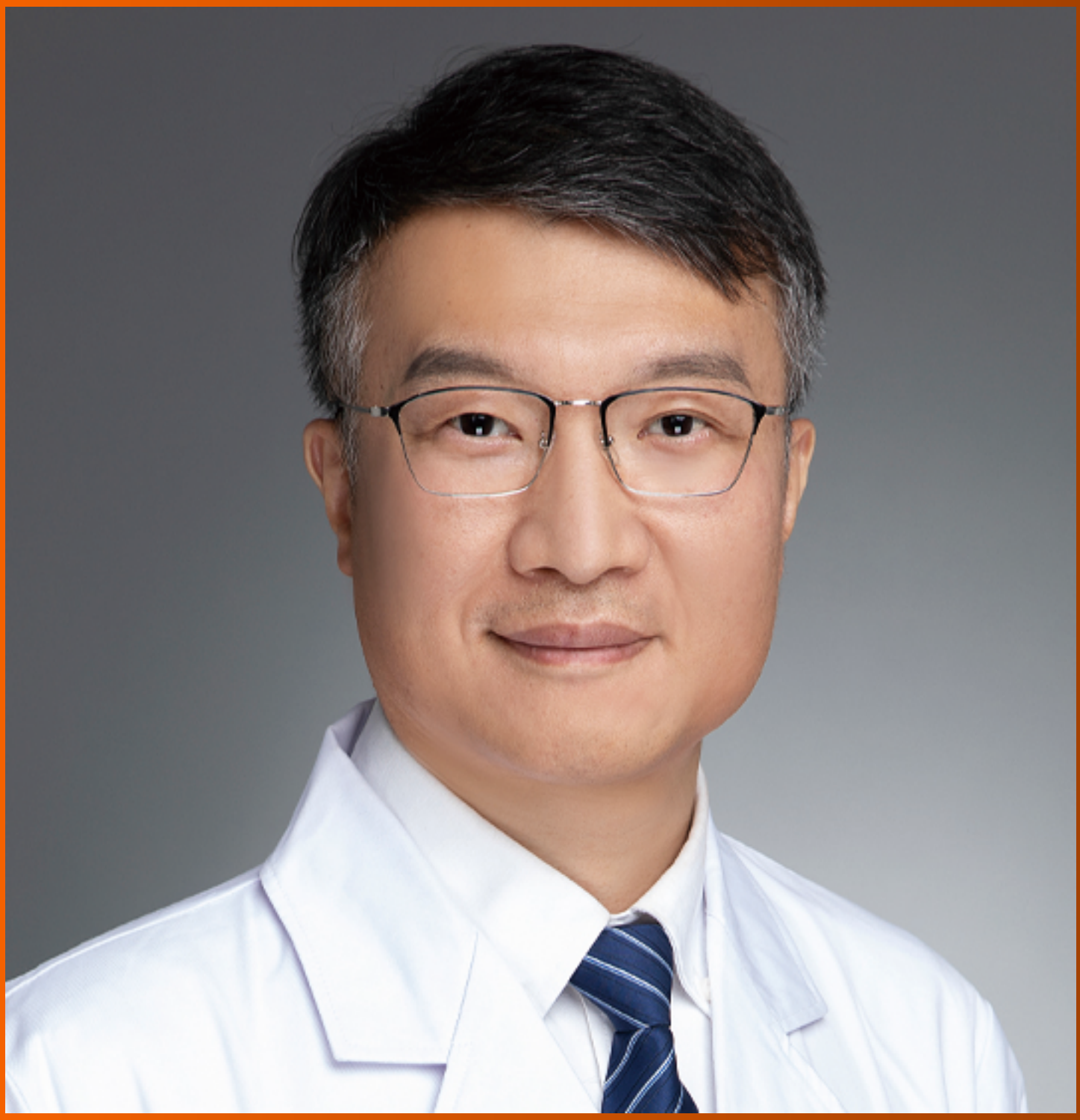

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AIMS AND SCOPE

The primary aim of *World Journal of Diabetes* (*WJD*, *World J Diabetes*) is to provide scholars and readers from various fields of diabetes with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

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MINIREVIEWS

Role and function of granin proteins in diabetes mellitus

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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, CgA_{10-19}, and CgA_{43-52} 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

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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.

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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 (CgA_{1-128})[21], vasostatin-I (CgA_{1-76}) and catestatin (CST, $CgA_{352-372}$) are found in beta cells; pancreastatin (PST, $CgA_{250-301}$) 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

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-19[1]	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)

[1]HISL-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.

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

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

Granin protein	Cleavage product
CgA[1]	Vasostatin-I (CgA_{1-76}) and -II (CgA_{1-115})
	Betagranin (CgA_{1-128})
	CgA_{10-19} and CgA_{43-52}[1]
	Chromofungin (CgA_{47-66})
	Vasoconstriction-inhibiting factor (CgA_{79-113})
	Chromostatin ($CgA_{124-143}$)
	Chromacin ($CgA_{173-194}$)
	Pancreastatin ($CgA_{250-301}$)[1]
	WE-14 ($CgA_{324-337}$)[1]
	Cateslitin ($CgA_{344-358}$)
	Catestatin ($CgA_{352-372}$)[1]
	Parastatin ($CgA_{357-428}$)
	GE-25 ($CgA_{367-391}$)
	Serpinin ($CgA_{417-442}$)
CgB[1]	CgB_{1-41}
	GAWK ($CgB_{420-493}$)
	BAM-1745 ($CgB_{579-593}$)
	PE-11 ($CgB_{555-565}$)
	Secretolytin ($CgB_{647-657}$)
	43kDa large CgB fragment
SgII[1]	Secretoneurin (conjugate of $SgII_{133-151}$ and $SgII_{154-186}$)
	EM66 (66 amino acid long)
	Manserin ($SgII_{497-536}$)
SgIII[1]	–[2]
HISL-19	–[2]
7B2	–[2]
NESP55	LSAL ($NESP55_{159-162}$)
	GAIPIRRH ($NESP55_{234-241}$)
VGF	Neuroendocrine regulatory peptide-1 ($VGF_{281-306}$)
	Neuroendocrine regulatory peptide-2 ($VGF_{310-347}$)
	NAPP129 or VGF20 ($VGF_{417-617}$)
	TPGH ($VGF_{422-430}$)
	TLQP-21 ($VGF_{556-576}$)
	TLQP-62 or VGF10 ($VGF_{556-617}$)
	HHPD-41 ($VGF_{576-617}$)
	AQEE-11 ($VGF_{588-599}$)
	AQEE-30 ($VGF_{588-617}$)
	LQEQ-19 ($VGF_{599-617}$)
proSAAS	KEP ($proSAAS_{1-7}$)
	Big SAAS ($proSAAS_{1-26}$)
	Little SAAS ($proSAAS_{9-26}$)

	GAV
	PEN (proSAAS$_{188-209}$)
	PEN-LEN (proSAAS$_{188-227}$)
	Little LEN (proSAAS$_{212-221}$)
	Big LEN (proSAAS$_{212-227}$)

[1]Granins and their cleavage products involved in carbohydrate metabolism.
[2]No 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.

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 alpha$_2$-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 there are 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 CgA$_{10-19}$ and CgA$_{43-52}$.

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 (HbA_{1C}) 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 HbA_{1C} 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 ($CgA_{324-337}$)[7], CgA_{10-19}, and CgA_{43-52}[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, CgA_{10-19}, and CgA_{43-52} 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 CgA_{29-42} 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 ($HbA_{1C} \geq 7.0\%$)[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 80% 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 is 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 has been found in DR patients compared with retinopathy originating in patients without diabetes. 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 continuously extends, 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.

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