Trends in Endocrinology & Metabolism

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REVIEWS

Opinion

Veiled Potential of Secretagogin in Diabetes: Correlation or Coincidence?

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Secretagogin (SCGN) is a calcium sensor protein enriched in neuroendocrine cells in general and pancreatic β-cells in particular. SCGN regulates insulin secretion through several Ca^{2+}-dependent interactions. Recent studies implicate SCGN in the β-cell physiology and extracellular insulin function, making it an intriguing candidate in diabetes research. Here, we propose a conjoining theme of diversified SCGN function in diabetes pathology. In our opinion, SCGN is an attractive therapeutic candidate ascribed by its role in β-cell maintenance and neuronal functions and in the efficacy of insulin. To scrutinize the therapeutic prospects of SCGN, we abridge putative diabetes-related properties of SCGN and put forth strategies to determine the precise role of SCGN in the pathogenesis/preclusion of diabetes.

Highlights

Secretagogin (SCGN) is a calcium sensor protein with the highest expression in pancreatic β-cells to regulate insulin expression and secretion.

Diabetic patients have reduced SCGN levels. In mice, lack of SCGN causes glucose intolerance and pancreatic β-cell depletion, while exogenous injection impedes these symptoms.

Several brain regions express SCGN for an unidentified purpose. In the hypothalamus, SCGN regulates CRH release to manifest stress response and activate HPA axis of systemic metabolic control.

A consolidated understanding of diverse SCGN expression/function is lacking. We present a comprehensive view of current knowledge in the field and discuss future directions to resolve the opacity in perplexing diabetes nexus and imminent therapeutic prospects.

As Medical Invention Advances, So Does Diabetes

Current scientific advancements and innovations are largely directed towards making human living standard healthier and superior. Paradoxically, a luxurious, sedentary lifestyle precipitates diabetes risk factors such as obesity, insulin resistance, and diabetes [1,2], creating a futile cycle of betterment and deterioration for millions of subjects. Moreover, the influence of the genetic makeup and epigenetic dynamics complicate our current systematic understanding of the pathogenesis and progression of diabetes. To confront multifactorial diseases such as diabetes, we need to adopt a strategy to study the holistic mechanism of pathophysiology and pursue knowledge-guided therapeutic discovery and development. However, unlike the problems of defined molecular mechanism and consequence (such as the prostaglandin synthase inhibition and pain relief [3]), we cannot anticipate a universal anti-diabetic medicine not only because of the multifactorial nature of the disease but also because of the variable individual response and drug–drug interaction in case the subject has to be treated for other illness in parallel. Therefore, considering the estimated increase in the diabetes patients in the coming years [4,5], the best strategy will be to discover, develop, or design as many anti-diabetic drugs as we can. But instead of a wild guess and blind explorations, a targeted and subjective selection of less studied potential leads appears to be a more viable alternative in terms of both temporal urgency and economic constraints.

Altered calcium and calcium sensor protein levels are implicated in diabetes genesis and progression [6–11]. Studies on several candidate proteins such as calcium-sensing receptor (CaSR) [8,12,13], tissue-specific calcium-regulated proteins [14,15], calcium channel [16], or calcium-dependent enzyme [17] have shown interesting metabolic phenotypes. This led to a promising study on the application of calcilytic therapy to rectify hypoglycemia in a CaSR-activating mutation carrying mice model [13]. However, the phenotypes of these candidate proteins are conditional and spatiotemporally limited. For therapeutic application, a soluble and injectable protein is preferred, but a potentially useful circulating calcium-sensor is unidentified.

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By the coordinated action of these diverse calcium regulatory proteins, the intracellular and extracellular calcium concentration is maintained within a permissible range [10,18]. A deviation from this physiological normality leads to the chaotic calcium signaling culminating at pathological conditions including diabetes [6–8,10]. Ca^{2+} is indispensable for every cell but **β-cells** (see Glossary) use it very determinedly [10,11]. Almost all aspects of β-cell biology are directly regulated by calcium signaling [11]. Ca^{2+} is crucial not only for regulated insulin release [19] but also for insulin synthesis and maturation [10,20]. Therefore, deregulated Ca^{2+} handling in β-cells causes impaired insulin synthesis, maturation, secretion, and function [10,11,19,20] that may culminate at diabetes [6,7,10,11]. A comprehensive understanding of Ca^{2+} regulatory proteins and events would advance our interpretation of the pathology and may offer futuristic restorative leads. Unfortunately, the precise molecular identity of extracellular and intracellular calcium regulators and a comprehensive understanding of Ca^{2+}-regulated events in the context of diabetes is not discerned. In this connection, **secretagogin** (SCGN) ranks first among the unexplored endogenous calcium sensor predicted to be implicated in insulin biosynthesis and action and in diabetes.

SCGN Is an Atypical Ca^{2+} Sensor

SCGN is a unique Ca^{2+} sensor protein with diverse tissue distribution, intracellular localization in neuroendocrine cells, and existence in extracellular milieu [21,22] (Figure 1). In the very first report, Wagner *et al*. suggested a positive role of SCGN in insulin expression and release [21]. The presence of extracellular SCGN in cultured cell supernatant was intriguing, but the biological significance remained unappreciated. After an extended latency in the SCGN-centric studies, the interest in SCGN appears to be reviving. Several studies reported insight into the mechanism of SCGN-mediated regulation of insulin secretion and suggested the important interaction of SCGN with the exocytosis component SNAP25 [23]. Later studies revealed several other SCGN-regulated events [24] including actin remodeling to control focal adhesion of insulin granules [25]. Besides insulin, corticotropin-releasing hormone (CRH) and matrix metalloprotease-2 have emerged as interesting hormones regulated by SCGN [26,27], with conceivably remarkable physiological implications. Although these studies provide unprecedented insight into the role of SCGN in hormone secretion, other cellular and extracellular roles of SCGN remain unknown. Lately, a multifaceted theme is evolving in terms of SCGN-mediated control of metabolism besides insulin secretion. Several observations suggest (i) non-exocytotic functions of SCGN in pancreatic β-cells, (ii) extracellular functions of SCGN in modulating insulin function, and (iii) perceived brain centric role of SCGN in regulating systemic metabolism.

Non-exocytotic Functions of SCGN in Pancreatic β-Cells

Insulin deficiency is a hallmark of type 1 diabetes mellitus (T1DM) and is also manifested in late type 2 diabetes mellitus. To therapeutically retain sufficient endogenous insulin synthesis, several strategies are being tested such as β-cell proliferators, stem cell therapy, and even *in vivo* trans-differentiation [28]. However, long-term insulin synthesis and β-cell maintenance are challenging. No single candidate gene is sufficient to deliver a sustained insulin synthesis and β cell maintenance for therapeutic applications. We consider SCGN as a promising candidate. Endogenous SCGN positively modulates insulin expression [21,29] and increases proliferation and physiological maintenance of β-cells [29]. To add to the credibility, SCGN knockout mice fail to develop sufficient β-cells due to compromised differentiation of progenitor cells [30]. Thus, SCGN emerges as an attractive candidate for gene therapy and incremental trans-differentiation factor along with previously described NPM (Neurogenin-3, Pdx-1, and MafA) factors [31], although it has a long way to go. Besides the role of endogenous SCGN in stabilizing islet mass and insulin synthesis, the exogenous recombinant protein is therapeutically very promising. As a proof of principle, administration of recombinant SCGN into β-cell-

Glossary

Adipokine: hormone synthesized and secreted by adipocytes to communicate the adipose energy status to the rest of the body. Leptin is the most studied adipokine that has a profound role in satiety. Adiponectin is another adipokine of well-recognized significance in glycemic control.

β-cell: a special type of cell in the pancreatic islets of Langerhans that synthesizes insulin and secretes it upon encountering a high glucose concentration.

HPA axis: a pathway of cross-organ communication wherein hypothalamus, pituitary, and adrenal cortex work in sync to cope up with a stress and to control systemic energy homeostasis. On encountering a stress signal, the vasopressin and CRH released from the hypothalamus is transported to the pituitary to induce the release of adrenocorticotropic hormone that diffuses to the adrenal cortex to stimulate secretion of glucocorticoid hormones including cortisol. Glucocorticoid hormones integrate the energy status and psychosocial cues to manifest an adaptive response.

Secretagogin: a Ca^{2+} sensor protein having six putative EF-hands for Ca^{2+} binding. Because of abundant pancreatic expression, it was first cloned by Wagner *et al*. [21] and was found to enhance insulin secretion.

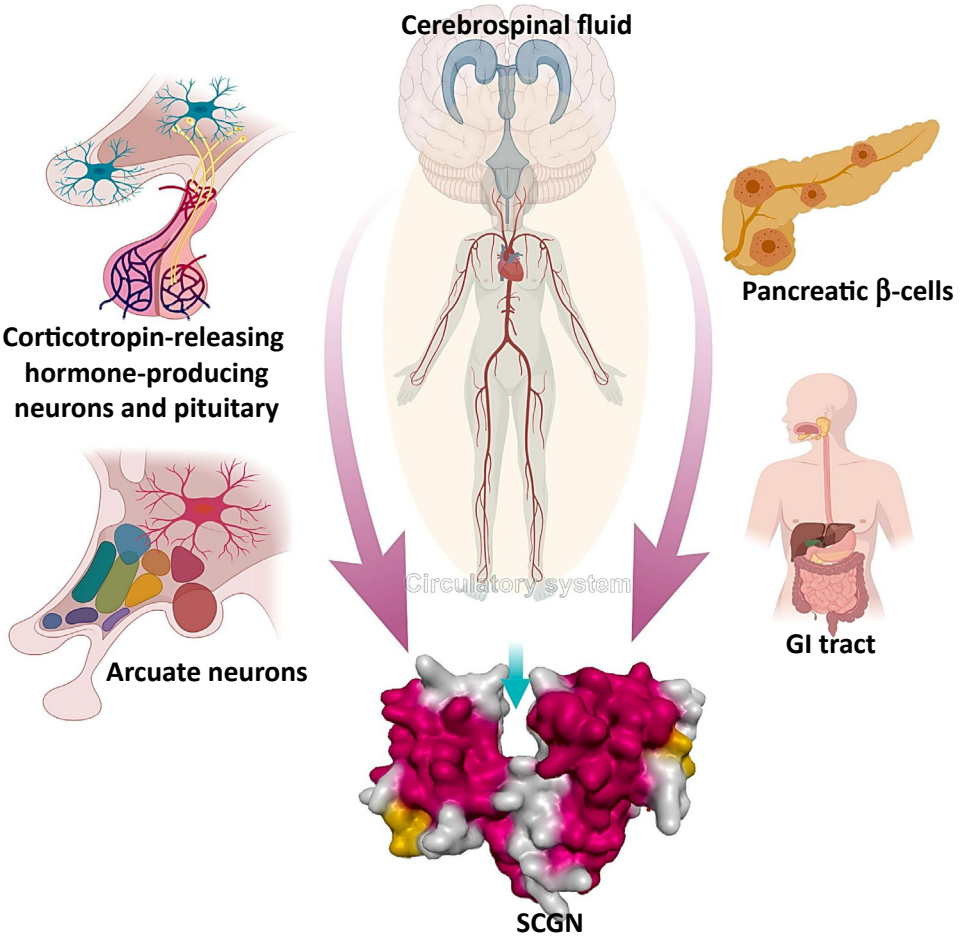

Figure 1. Diverse Tissue Expression and Varied Molecular Properties Make SCGN Multifaceted. Many tissues (including pancreatic, gastrointestinal (GI) tract, hypothalamus, pituitary, and arcuate nucleus) synthesize endogenous secretagogin (SCGN), while the cerebrospinal fluid (CSF) and circulatory presence make SCGN pervasive. However, for many tissues (such as the arcuate nucleus), the functional consequence of SCGN expression is unknown. Once a cell synthesizes SCGN, the biological availability and function are governed by the molecular properties of SCGN (such as the oligomeric status or Ca^{2+} availability). Owing to the number of possible combinations of these factors and other interacting partners, the spatiotemporal regulation of SCGN action is imaginably multi-layered. Moreover, a prominent conformational groove in SCGN (indicated by an arrow in the SCGN model) might act as a hydrophobic binding site for small molecules/peptide hormones.

deficient mice induces perceivable regeneration of pancreatic islets along with insulin expression [32]. It is of immediate interest to perform lineage tracing experiments [31] to delineate the origin of SCGN-induced β-cells and to quantitate the efficiency of regeneration. Although the fundamental role of SCGN in insulin synthesis, maintenance, and regeneration seems reliable, as these findings are validated in several unrelated studies, comprehensive studies are required to scrutinize/validate the therapeutic potentials.

Extracellular Functions of SCGN

The activity of several circulatory peptide hormones is modulated by cognate hormone binding proteins [such as insulin-like growth factor binding proteins (IGFBPs) for insulin-like growth

factors, CRH binding protein for CRH, etc.]. By contrast, insulin activity is primarily regulated by controlled and pulsatile release of insulin from islets [33] and receptor-mediated internalization and degradation of circulating insulin in the liver [34]. The physiological modulation of plasma insulin interaction with its receptor is poorly understood, except for the moonlighting insulin binding activity of IGFBPs [35,36]. Fresh insight originates from recent studies that indicate that the extracellular SCGN may act as a modulator of insulin action in circulation. Two independent but complementary reports suggest a role for intracellular SCGN [29] or extracellular SCGN [32] in modulating physiological insulin efficacy. Malenczyk *et al*. reported downregulation of pancreatic SCGN in diabetic human subjects. They described a negative correlation between pancreatic SCGN expression and glycated hemoglobin (HbA1c) and a positive correlation with insulin expression [29]. Because SCGN deficiency causes diabetes-like symptoms [29] and exogenous administration of recombinant SCGN resists diabetogenesis in high-fat diet (HFD)-fed mice [32], this suggests that SCGN is an anti-diabetic protein and that diabetes might be a state of SCGN deficiency. Consistently, SCGN knockout mice show impaired insulin response as evident from the glucose intolerance and progressive hyperglycemia [29]. However, it was unclear whether diabetes-associated downregulation is pancreas specific or systemic. Another intriguing aspect was to check whether a chronic exogenous supplementation of SCGN could preclude SCGN deficiency-associated decline in insulin efficacy. Supporting systemic insufficiency of SCGN, a significant reduction in circulating SCGN is noted in the HFD-fed mice. Administration of exogenous SCGN preserves insulin sensitivity and systemic health including improved cholesterol balance, reduced hepatic steatosis, and decreased lipid deposition [32]. In the retrospect, the conclusions are also supported by previous observation wherein obesity-inducing HFD-fed animals exhibit the downregulation of SCGN [37]. Similarly, downregulation of pancreatic SCGN was reported in diabetes-prone Goto-Kakizaki rats [38]. Thus, several independent studies indicate that diabetes is a state of systemic SCGN deficiency and therapeutic administration of SCGN may preclude diabetic complications.

Like any plasma protein, circulatory SCGN has access to almost all tissues and could potentially interact with multiple organs to influence systemic physiology directly or indirectly. Similarly, the circulatory SCGN has access to multiple circulating factors and hormones. Given the property of calcium sensor proteins to interact with multiple proteins and ligands, it also raises the possibility of many uncharted interesting interactions. The effect of SCGN on insulin signaling was studied recently [32]; however, whether SCGN binds and modulates other peptide hormones is unexplored. Considering SCGN as a functional circulatory protein raises several new questions. Does SCGN have a direct effect on target tissues? If yes, then how does SCGN differentiate between a target and non-target tissue? Does pancreatic SCGN (secreted from β-cells) have any effect on the neighboring αcell or the glucagon turnover? Besides these unanswered questions, the functional correlates of diverse subcellular localization of SCGN in the endoplasmic reticulum (ER), nucleus, and cytosol remain undeciphered. Also, being a Ca^{2+} sensor, how SCGN modulates intracellular Ca^{2+} concentration is not understood. It will be exciting to examine the circulatory interactome of SCGN and validate whether extracellular SCGN interacts with membrane Ca^{2+} channels to help maintain intracellular Ca^{2+} concentration.

Brain-Centric Role of SCGN in Regulating Systemic Metabolism

Many tissue/cell types express an appreciable amount of SCGN [21,22]. Interestingly, many of the (neuro)endocrine tissues that have a prominent regulatory effect on the systemic metabolism abundantly express SCGN (Figure 1). Moreover, cerebrospinal fluid (CSF) SCGN may affect the biology of other brain regions that do not express SCGN (Figure 1). Nonetheless, the biological correlates of the tissue-specific expression are not greatly appreciated. Multiple

genomic/proteomic data indicate that many of the neuronal and non-neuronal exocytosis active cells (such as glandular exocrine cells of pituitary, hypothalamic cell, pancreas, gut, and thyroid gland) show considerable SCGN expression [21,22] (also see Allen Mouse Brain Atlas experiment id 583549). A functional analogy may suggest a role of SCGN in hormone secretion, but the validation is due.

Hypothalamus is an important brain center involved in regulating whole-body metabolism by secreting various hormones that have a systemic homeostatic effect. Based on the expression of SCGN in hypothalamic paraventricular nucleus cells, SCGN was demonstrated to regulate CRH secretion in stress. However, it is important to evoke that besides the behavioral stress response, CRH prominently influences systemic metabolism through the activation of the **hypothalamic-pituitary-adrenal** (**HPA) axis** [39]. It is also interesting to note that all the tissue centers of the HPA axis (hypothalamus, pituitary, adrenal gland) are SCGN positive. The fundamental question is does SCGN modulate the synthesis or secretion of other HPA hormones (adrenocorticotropin and cortisol) from the respective glands? If so, why is the CRH regulation not sufficient? Or is SCGN deployed to exert multi-layered regulation of HPA axis? The SCGN-mediated regulation of the HPA axis in the background of metabolic stress (such as obesity) is expected to have a long-lasting impact on systemic metabolism and needs to be studied thoroughly.

The arcuate nucleus is another metabolically responsive brain region that exerts prime regulation on satiety and energy storage/homeostasis. The arcuate harbors a large SCGN-positive neuronal pool [26] (also see Allen Mouse Brain Atlas experiment id 583549). Given the profound effect arcuate neurons, specifically $POMC^+$ and NPY^+ neurons, have on the food intake and energy expenditure, it is intriguing to study the role of SCGN in arcuate-mediated systemic energy homeostasis. This becomes much more important when we consider recent reports suggesting the involvement of SCGN in obesity [32,40,41], a disorder of compromised food and energy homeostasis.

CSF baths many neuronal extensions of the hypothalamus and other regions. Altered CSF composition is linked to various metabolic complications including diabetes. It has been suggested that CSF forms a neuronal connective tissue and its composition reflects CNS health. SCGN is a component of CSF, and insulin-resistant (Alzheimer's) patients have reduced CSF SCGN concentration [42]. Cumulatively, it is apparent that the diabetes is a state of pancreatic [29], circulatory [32], and central [42] SCGN deficiency. Ironically, we have no clue about the physiological source of CSF/circulatory SCGN. Although pancreatic β-cells are one possible source as demonstrated *in vitro* [21], we have to presume that SCGN can cross the blood–brain barrier to reach the CSF. However, it is counterintuitive as to why would the SCGN will traffic from the pancreas to CSF if the brain itself synthesizes a good amount of SCGN. In such a scenario, finding the secretory source for SCGN becomes imperative. It is also vital to make a distinction between intracellular and extracellular functions of SCGN. Since the SCGN knockout model is already available, a simple strategy to study the effect of extracellular/circulatory SCGN will be to inject exogenous SCGN (at specific sites such as CSF injection using stereotaxic procedures or systemic injection by various routes such as subcutaneous or intraperitoneal) while the animals are in healthy conditions or when challenged with diabetogenic factors (as genetic models of diabetes, HFD, or streptozotocin). Nonetheless, owing to the multitude of regulatory variables (Figures 1–3), differentiation of the intracellular protein function from that of extracellular protein would be difficult (Figures 2 and 3). We should also explore for the SCGN-mediated neuronal regulation of metabolism and check whether SCGN administration (to re-establish the normal CSF concentration) could reverse the insulin resistance. However, before performing such intricate experiments, it will also be interesting to check whether SCGN can cross the blood–brain barrier in physiologically meaningful ways.

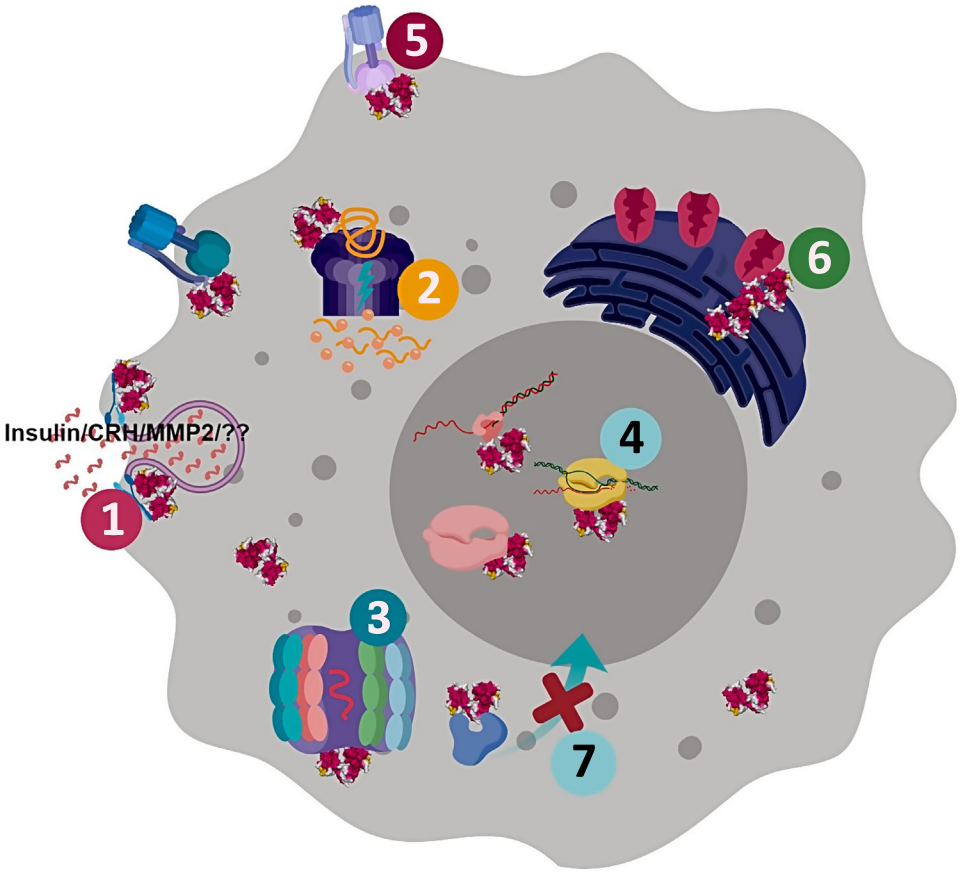

Figure 2. The Mechanistic Understanding of SCGN Function Is Limited. The mechanism of intracellular secretagogin (SCGN) action is manifold and the appreciation is far from complete. A few plausible modes of SCGN action are discerned. Based on reported interactions or subcellular localization, we classify the following established or plausible modes of SCGN action: (1) SNAP- and actin-mediated regulation of insulin secretion is well studied, but other possible modes of action remain unestablished. CRH, corticotropin-releasing hormone; MMP2, matrix metalloprotease-2. (2) Because of the large chaperone interactome, SCGN is proposed to work as a classical molecular chaperone. The chaperoning action of SCGN for insulin was demonstrated recently [32], but the identity of other clients remains unknown. (3) SCGN interacts with the proteasome components and protects Pdx1 from degradation [30], but the universality of this interaction remains untested. (4) A large fraction of SCGN localizes in the nucleus with unknown consequence. The possibility of direct DNA/transcription factor binding needs to be tested. (5) SCGN regulates intracellular Ca^{2+} concentration via an unknown mechanism [21]. The possibility of Ca^{2+} channel interaction remains unconfirmed. (6) SCGN has been shown to localize to the endoplasmic reticulum (ER) and is also implicated in ER stress, although the mechanistic insight is lacking. (7) There is untested possibility of SCGN-mediated control of the nuclear localization of specific transcription factors similar to calcineurin-mediated regulation of NFAT localization.

Nevertheless, compelling data suggest that brain SCGN plays a larger unappreciated role in controlling the systemic metabolic homeostasis and deregulated SCGN results in the progression of diabetes.

Many Moderators Concertedly Regulate SCGN Function

Tissue expression suggests a potential impact of a gene on the functioning of a given tissue. However, even after protein synthesis, there exist a variety of modulators that eventually control the function of a protein with spatiotemporal precision (Figure 3). In the case of SCGN, Ca^{2+}

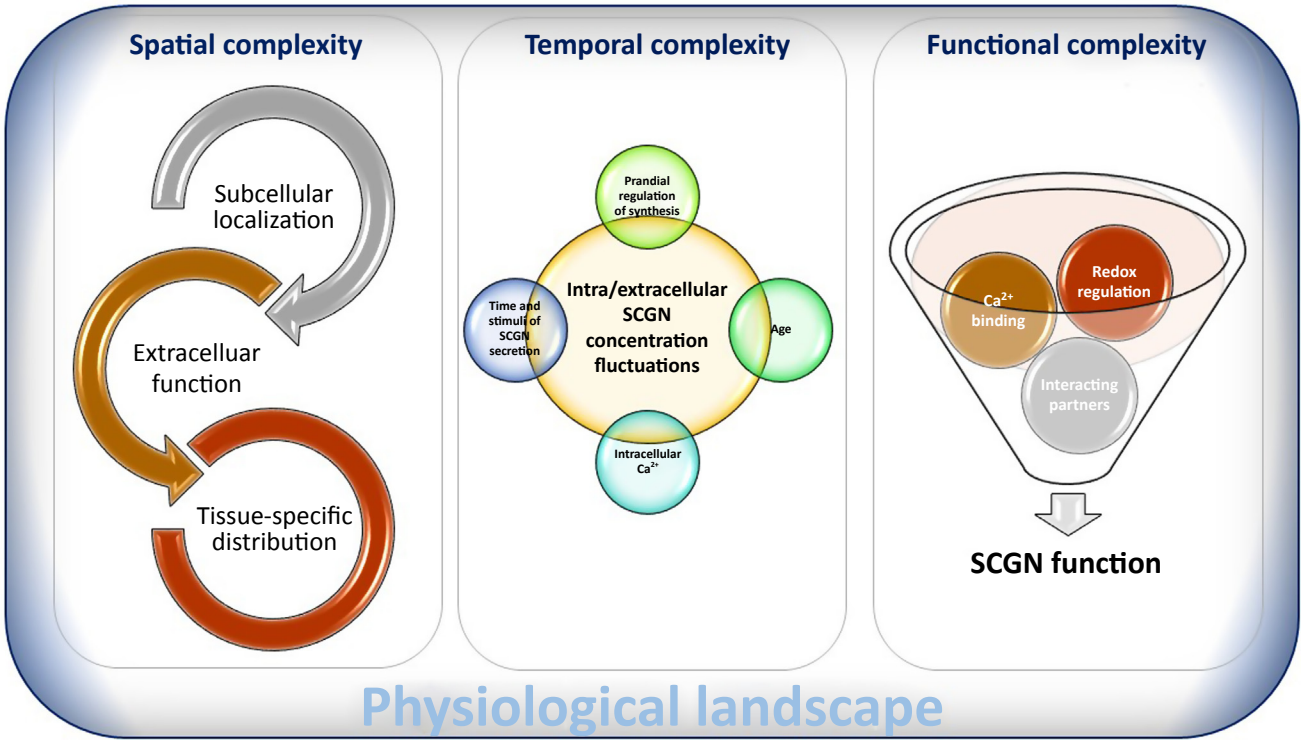

Figure 3. Unresolved, Multi-layered Regulation of SCGN Function. A multitude of variables regulate the functions of secretagogin (SCGN). A diverse intracellular and extracellular localization poses the primary challenge to differentiate between the function of cytoplasmic or subcellular depot-enriched protein. Another layer of intricacy originates from the poorly defined regulation of SCGN synthesis and secretion. Although SCGN promoter is glucose responsive [45], predictable prandial regulation of SCGN synthesis/secretion remains unknown. Recent reports suggested age-associated methylation of *SCGN* [56], but how this altered methylation affects SCGN expression and function is unestablished. Similarly, the effect of Ca^{2+} (the primary ligand for SCGN) on the SCGN localization and secretion is uncharted, although it is well established that Ca^{2+} regulate protein–protein interactions of SCGN. The cofactor binding, redox environment and the presence of SCGN-interacting proteins further complicate our comprehensive understanding of SCGN function. These numerous variables regulate the physiological activity of SCGN in a healthy subject. However, it is inconceivable now as to how a pathological condition (such as diabetes or neurodegeneration) will interact with these regulatory factors; hence, it is hard to imagine a direct consequence of morbidity on SCGN expression and function.

availability is the primary factor that regulates the properties and biochemical stability [23,43,44]. However, Ca^{2+} is certainly not the only modulator. Redox state and glucose availability are two other established modulators of SCGN [43–46]. It is important to note that all these factors are integral and vital part of the homeostatic machinery, and change in any one of these factors underwrites diabetes [6,7,10,47–49]. Several reports convincingly demonstrated that the redox condition in the surrounding milieu can also impact the SCGN function and properties by modulating the conformation and oligomeric status of the protein [43,44]. Similarly, peripheral glycemic status regulates the expression of SCGN to a large extent [29,32,50]. In the hyperglycemic condition, downregulation of SCGN at the cellular [50], tissue [29], and systemic [32] levels is already reported. The glycemic regulation of SCGN likely originates from a direct mechanism of glucose-sensitive expression of SCGN because SCGN promoter is glucose responsive [45]. Since SCGN is a component of ER homeostasis in β-cells [29], and hyperglycemia induces ER stress, a glucose-induced downregulation of SCGN could conceivably be one of the causal factors in the hyperinsulinemia-associated ER stress. Besides these direct modulators, there are numerous credible interacting partners that have a potential to modulate the protein activity based on the redox environment and Ca^{2+} availability (Figure 3).

Thus, the expression of SCGN in any cell hints at the possibility of its function; however, the activity is regulated much more intricately primarily by Ca^{2+}, redox, and glycemic conditions and conceivably by many other interacting partners.

Multifaceted SCGN Is Inherently Difficult to Comprehend

Ca^{2+} sensor proteins are intrinsically multifunctional. The versatility is bestowed by the hundreds of protein–protein (or other biomolecular) interactions that they undergo. For SCGN, the insulin secretory function can be well explained by its interaction with SNAP proteins and actin [23,25]. However, how SCGN regulates complex traits such as obesity, systemic metabolism, and β-cell regeneration is unappreciated. SCGN has been shown to modulate expression of a few genes [21], but the mechanism of gene expression regulation by SCGN is completely uncharted. Other Ca^{2+} sensor proteins, which are well-established regulators of transcription, use different mechanisms to regulate the gene expression. Calcineurin, for example, regulates gene expression by controlling the nuclear localization of a prominent transcription factor NFAT [51]. In contrast, DREAM (also known as KChIP3) directly binds to a specific DNA motif [downstream regulatory element (DRE)] and controls the expression of DRE-containing genes [52]. For SCGN, no explicit mechanism has been discerned despite the fact that the transcription modulatory effect of SCGN (on insulin and TAC gene expression) was observed ever since SCGN was first cloned [21]. Although the intracellular phenotypes could be speculated to be originating from the protein–protein interaction, how extracellular SCGN communicates through the interior of the cell is an unsolved mystery. Several possibilities exist for how SCGN communicates from the exterior of the cell; in our opinion, more than one mode could be true. While the presence of SCGN-specific cell surface receptor seems unlikely, a moonlighting SCGN binding to other cell surface receptor cannot be ruled out.

SCGN Is Involved in Obesity by an Unknown Mechanism

Obesity and hyperinsulinemia are interdependent risk factors for diabetes [53]. Secretagogin seems to regulate both; however, which is the primary responder of SCGN is not established. Secretagogin is a recognized player in insulin synthesis and secretion; however, whether SCGN has regulatory control on the obesity/type 2 diabetes-associated hyperinsulinemia and T1DM-associated hypoinsulinemia is unknown. Since hyperinsulinemia is apparently both the cause and consequence of obesity [53], the role of SCGN in establishing obesity would be interesting to study. For this purpose, the effect of a diabetogenic diet (high fat and high fructose) in control versus SCGN knockout animals need to be studied both at a phenotypic and (molecular) mechanistic levels. The SCGN locus is associated with bodyweight biological trait [40,41]; nonetheless, the precise role of SCGN in controlling body weight is unknown. In a recent study, the SCGN was found to be upregulated in the cells treated with adipogenic factors [54]. Upregulation of a gene could be to counter the change or to favor the change. Therefore, the role of SCGN on cellular lipid accumulation remains inconclusive. SCGN promoter has a predicted peroxisome proliferator-activated receptor gamma regulatory element [55], and measurable SCGN transcripts are reported in adipose tissue (human protein atlas). This suggests that SCGN may also control the release of leptin and other **adipokines**. However, this is completely a naïve field and before venturing into it, one has to categorically explore the spatiotemporal regulation of SCGN expression and identify the responsible transcription factors.

Concluding Remarks and Future Perspectives

The SCGN is certainly an intriguing lead in the field of diabetes pathophysiology. It regulates many critical events in the insulin signaling pathway from transcription to extracellular function. Diabetes-associated downregulation of SCGN is cited by several independent reports, raising its credibility. However, until now only basic biologists have been working in this field, which

Outstanding Questions

How does SCGN regulate insulin gene expression? Is nuclear localization of SCGN biologically relevant?

What is the physiological source of circulatory/CSF SCGN? How does extracellular SCGN communicate with the interior of the target cell? How does SCGN discriminate target cells from non-target cells?

How does SCGN regulate complex traits such as obesity, systemic metabolism, and β-cell regeneration?

Does SCGN influence systemic metabolism through the HPA axis?

Does SCGN regulate the release of proopiomelanocortin/neuropeptide Y hormones from the arcuate nucleus?

Can external SCGN supplementation alleviate pre-established diabetes?

limits the availability/understanding of the clinical data and therapeutic possibilities. Nonetheless, stimulating data reported in past 2 years will invoke a fresh interest among the biologists and clinicians to prioritize the studies on the metabolic and physiological attributes of SCGN and also to scrutinize and optimize the therapeutic potential (if any) of SCGN. A few experiments of immediate interest are presented in Outstanding Questions.

Author Contributions

A.K.S. conceptualized the outline. A.K.S. and R.K. discussed the content and drafted the manuscript/artwork. A.K.S., R. K. and Y.S. contributed to the manuscript editing/revision.

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