Function and Expression of Somatostatin Receptors of the Endocrine Pancreas

Mathias Z. Strowski, Allan D. Blake

Title: Function and Expression of Somatostatin Receptors of the Endocrine Pancreas

Authors: Mathias Z. Strowski, Allan D. Blake

PII: S0303-7207(08)00068-3
DOI: doi:10.1016/j.mce.2008.02.007
Reference: MCE 6819

To appear in: *Molecular and Cellular Endocrinology*

Received date: 31-5-2007
Revised date: 3-2-2008
Accepted date: 12-2-2008

Please cite this article as: Strowski, M.Z., Blake, A.D., Function and Expression of Somatostatin Receptors of the Endocrine Pancreas, *Molecular and Cellular Endocrinology* (2007), doi:10.1016/j.mce.2008.02.007

Function and Expression of Somatostatin Receptors of the Endocrine Pancreas

Mathias Z. Strowski[1]* and Allan D. Blake[2]

[1]Medizinische Klinik mit Schwerpunkt Hepatologie und Gastroenterologie, Interdisziplinäres Stoffwechsel-Centrum: Endokrinologie, Diabetes und Stoffwechsel, Charité - Universitätsmedizin Berlin, Germany

[2]Department of Biological Sciences, Seton Hall University, South Orange, New Jersey, USA

***Corresponding author:**

Mathias Z. Strowski, MD
Medizinische Klinik m. S. Hepatologie, Gastroenterologie
& Interdisziplinäres Stoffwechsel-Centrum/Endokrinologie und Diabetes mellitus
Charité - Universitätsmedizin Berlin
Campus Virchow-Klinikum
Augustenburger Platz 1
13353 Berlin
Germany
Tel.: +49 (030) 450 559 066
Fax: +49 (030) 450 559 966
Email: mathias.strowski@charite.de

Keywords: insulin, glucagon, endocrine islets, pancreas, somatostatin, receptor, secretion

Disclosure

The authors have nothing to disclose

Acknowledgment

MZS was supported by a research grant from the Deutsche Forschungsgemeinschaft (STR558/4-1 and 4-2) and the Sonnenfeld-Stiftung.

Content

Abstract

Somatostatin (SST) regulates multiple biological processes via five genetically distinct, G-protein coupled receptors. Clinical interest in therapy for neuroendocrine and metabolic disorders has resulted in the development of new tools for exploring the function of somatostatin receptors (SSTRs). The development of highly SSTR-selective agonists and antagonists, animal models with the deletion of individual SSTRs, as well as SSTR-specific antibodies have all been utilized in delineating SSTR functions. In the pancreas, SST is a potent regulator of insulin and glucagon secretion. Indeed, the inappropriate regulation of pancreatic A- and B-cell function in metabolic diseases provides an impetus to evaluate the SSTRs as therapeutic targets. By combining the results obtained from molecular biology, pharmacology and immunochemical studies the current review provides a summary of important recent developments which have extended our knowledge of SST actions in the endocrine pancreas.

Structural organization, physiology of the endocrine pancreas and its relationship to somatostatin

The adult human pancreas contains approximately 100,000 – 1,000,000 endocrine islets, occupying approximately 1% of the whole organ. The individual islets are composed of at least 20 hormonally active cell types. The four major endocrine cell types are A-, B-, D-, and PP-cells which secrete glucagon, insulin, SST or pancreatic polypeptide, respectively.

Pancreatic B-cells comprise approximately 60-70% of the islet cells, followed by PP- (15%-34%), A- (10%-26%), and D-cells (5%-8%) (Stefan et al., 1983; Iki and Pour 2007). The distribution of endocrine active cells within pancreatic islets differs between species. In rodents, B-cells are located in the central part of the islets, whereas the periphery contains mostly A-, D-cells and PP-cells (Samols et al., 1986; Samols et al., 1988; Samols and Stagner 1990). In contrast, all four hormonally active cell types in humans and pigs are randomly distributed throughout the pancreatic islets (Cabrera et al., 2006).

SST tightly controls the secretion of glucagon and insulin, two major hormones regulating glucose homeostasis. There are two major circulating SST-isoforms, which consist of 14 and 28 amino acids, respectively, which are processed from a common precursor protein in a cell- and tissue-specific pattern (Brazeau et al., 1973; Burgus et al., 1973; Pradayrol et al., 1980). In the adult, the primary secretory product of pancreatic D-cells is SST-14 (Noe 1981; Patel et al., 1981), which contributes to less than 5% of circulating SST (Taborsky, Jr. and Ensinck 1984). In the fasting state plasma concentration of SST is low (30-100 pg/ml) and increases by approximately two-fold in the postprandial state (Binimelis et al., 1987). This postprandial increase is mostly due to increased circulating SST-28, that is derived from the intestinal epithelium (Patel and O'Neil 1988; Baskin and Ensinck 1984). Among the stimuli of SST secretion from intestinal and pancreatic D-cells, glucose, amino acids such arginine, isoleucine, as well as, ketone bodies, and hormones (CCK, gastrin, secretin) were identified (Hermansen 1980). Insulin stimulates SST secretion at high glucose concentrations, only (Brunicardi et al., 2001). Since SST can directly suppress insulin synthesis and release (see below), it appears that insulin clamps its own secretion by stimulating SST release.

Paradoxically, the secretion of SST increases following a lowering of blood glucose concentration (Schauder et al., 1979), which might be explained by glucagon-mediated stimulation of D-cell activity (Patton et al., 1977). This theory is supported by the recent finding that glucagon together with L-glutamate, an amino-acid which is co-secreted from pancreatic A-cells, can together stimulate pancreatic SST secretion at low glucose (Muroyama et al., 2004). Also an activation of beta-adrenergic system by hypoglycemia may also lead to increased secretion of SST (Kanatsuka et al., 1981; Hermansen 1980). Taken together, there seems to be a negative feedback between glucagon and SST release and insulin and SST interaction.

In addition to its potent antisecretory activity, SST inhibits gene expression of insulin, glucagon and PP (Efendic et al., 1978; Kleinman et al., 1995; Moller et al., 2003; Koerker et al., 1974; Philippe 1993; Fehmann et al., 1995; Kendall et al., 1995). The effect of SST on insulin output appears to be direct and

for a large part due to extrapancreatic sources of SST, in that pancreatic B-cells preferentially bind SST-28 (Mandarino et al., 1981). However, paracrine mechanisms of SST-14 action on A-, B, and D-cells have also been proposed (Samols and Stagner 1990; Taborsky, Jr. 1983).

Despite the lack of convincing evidences that SST has intrinsic effect on carbohydrate metabolism there are numerous studies demonstrating that SST plays an important role in modulating glucose homeostasis through interaction with pancreatic A- and B-cells (Unger and Orci 1977). It has been postulated that the postabsorptive increase of SST secretion may provide a mechanism to prevent excessive glucagon secretion (D'Alessio et al., 1989; Klaff and Taborsky, Jr. 1987). However, the role of pancreatic SST in inhibiting glucagon secretion may be more relevant in the basal state, because anti-SST enhanced glucagon output from the perfused human pancreas only at low glucose concentrations (Brunicardi et al., 2001; Kleinman et al., 1994). The physiological relevance of the inhibition of insulin secretion by SST at high glucose could be a prevention of postabsorptive insulin hypersecretion, providing a mechanism to protect against development of postprandial hypoglycemia.

The mechanisms, by which SST reduces glucagon and insulin secretion, involves priming of secretory granule release (Gromada et al., 2001), reduction of intracellular calcium levels (Nilsson et al., 1989), as well as modification of cellular glucose metabolism and oxidation (Daunt et al., 2006).

Somatostatin and diabetes mellitus

Alteration of somatostatin expression

Type 1 diabetes mellitus

Patients with type 1 diabetes were reported to have increased number of D-cells, whereas the ratio of D- to A-cells was decreased due to A-cell hyperproliferation (Orci et al., 1976; Rahier et al., 1983). Type 1 diabetic patients had elevated basal plasma SST concentrations (Skare et al., 1985; Segers et al., 1989) and increased responsiveness of pancreatic D-cells to arginine, whereas the overall prandial SST levels was reduced (Skare et al., 1985). Treatment with insulin normalized the elevated basal plasma SST levels in these patients (Segers et al., 1989). Animals with streptozotocin-induced diabetes and NOD mice with autoimmune diabetes have increased size and number of D-cells as well as increased pancreatic SST content (Orci et al., 1976; Gomez Dumm et al., 1995; Kanatsuka et al., 1981). Administration of insulin also reduced the elevated levels of pancreatic SST and glucagon content in Sprague-Dawley (Papachristou et al., 1989) and Wistar (Kadowaki et al., 1980) rats with streptozotocin-induced diabetes and in dogs with alloxan-induced diabetes (Rastogi et al., 1990). It is important to note that at least in animal models with chemically-induced type 1 diabetes, pancreatic D-cells show reduced or no response to increased glucose, which may explain the inadequate increase of SST secretion following food ingestion (Grill and Efendic 1983; Hermansen 1981). The preserved secretory response of D-cells to arginine and other nutrients, suggests a selective loss of glucose-sensitivity in type 1 diabetes mellitus (Ostenson et al., 1990).

The cause of elevated SST in type 1 diabetes remains to be determined, where many factors including chronic exposure of D-cells to hyperglycemia, ketone bodies, hyperglucagonemia or lack of circulating insulin may be involved. Also, the functional relevance of increased SST expression in type 1 diabetes remains unknown. It is possible, that the chronic SST hyperproduction in type 1 diabetes may protect the organism from extreme hyperglucagonemia. On the other hand, increased basal SST secretion could further deteriorate the severity of type 1 diabetes, by inhibiting insulin secretion from the residual pancreatic B-cells. Lastly, an inadequate release of SST in response to food ingestion may explain the excessive glucagon secretion in patients with type 1 diabetes.

Type 2 diabetes mellitus

In patients with type 2 diabetes the number of A- and D-cells is increased (Iki and Pour 2007), whereas the ratio of D- to A-cells is decreased (Rahier et al., 1983; Iki and Pour 2007). Pancreatic SST content of spontaneously diabetic adult ob/ob and db/db mice is increased (Makino et al., 1979). Patients with impaired glucose tolerance (IGT) and type 2 diabetes have SST levels similar to that of controls (Skare et al., 1985; Gutniak et al., 1986; Segers et al., 1989). However, the rise in SST in response to food ingestion or challenge with exogenous glucose is markedly reduced (Skare et al., 1985; Gutniak et al., 1986), while insulin treatment can restore the SST response to hyperglycemia (Gutniak et al., 1989). Intravenous infusion of tolbutamide, a powerful stimulus of insulin and SST secretion (Ipp et al., 1977), resulted in a biphasic increase in plasma SST in both healthy volunteers and patients with IGT, while patients with type 2 diabetes failed to respond to tolbutamide administration (Segers et al., 1989). Type 2 diabetic patients with normal basal insulin levels had normal fat-stimulated SST secretion (D'Alessio and Ensinck 1990), indicating that physiological insulin concentration is prerequisite to achieve an adequate increase of SST secretion.

Overall, both type 1 and type 2 diabetic patients have increased number of D-cells, reduced ratio of D- to A-cells and impaired glucose-stimulated SST secretion. The basal SST concentration in type 1 diabetes is increased, but normal in type 2 diabetes. Whether insulin (absent in type 1 diabetes) is the crucial factor responsible for the differences of SST secretion between type 1 and type 2 diabetes remains to be determined.

However, based on the data on patients with IGT, type 1 and type 2 diabetes, it is likely that insulin is required to preserve a physiological function of pancreatic D-cells. One of the mechanisms may include restoration of the glucose sensitivity in pancreatic D-cells, however this mechanism has not yet been demonstrated.

Somatostatin in therapy of diabetes mellitus

Both type 1 and type 2 diabetic patients have impaired glucose-stimulated SST secretion which might contribute to impaired prandial suppression of glucagon (Unger and Orci 1975; Unger 1976; Unger 1975; Shah et al., 1999; Reaven et al., 1987). Hyperglucagonemia further exacerbates hyperglycemia

through stimulation of hepatic glucose production (Ohneda et al., 1978; Dinneen et al., 1995; Shah et al., 2000; Unger and Orci 1975; Unger 1975). The immunoneutralization of the endogenous glucagon, administration of glucagon receptor antagonists, reduction of glucagon receptor expression or the deletion of glucagon receptors leads to a reduction of hyperglycemia in diabetic animal models (Brand et al., 1994; Liang et al., 2004; Gelling et al., 2003). Given the potential for SST to inhibit glucagon secretion it has been considered as adjunct therapy with insulin to treat diabetes (de Laszlo et al., 1999; Petersen and Sullivan 2001; Madsen et al., 2002).

Type 1 diabetes mellitus - Early studies have demonstrated that a continuous delivery of SST as adjunct to insulin treatment reduced the amount of exogenous insulin required to maintain normoglycemia in type 1 diabetic patients (Gerich et al., 1974; Gerich et al., 1977). These beneficial effects of SST on glucose control were attributed to the ability of SST to suppress glucagon secretion (Liljenquist et al., 1979). Although it has not been directly studied, SST treatment may also improve insulin sensitivity by lowering elevated GH levels, which are known to impair insulin signaling (Takano et al., 2001; Hansen et al., 1986). However, the beneficial effect of SST on glucose homeostasis does not appear to extend across species (or experimental models). Specifically, continuous treatment of severely diabetic Balb/C mice with octreotide did not influence blood glucose or insulin levels, however it reduced GH hypersecretion and prevented the proliferation of kidney glomeruli (Rastogi et al., 1990). Octreotide did not reduce hyperglycemia in alloxan-diabetic male Wistar rats, however a reduction of kidney weight without normalization of the glomerular filtration rate was reported (Usenmez et al., 2000). Although in type 1 diabetic rats, circulating GH levels are reduced, treatment with SST may further suppress GH output and contribute to changes in kidney size, or SST may have direct effects on kidney IGF-I production, as well as altering IGF binding protein concentrations (Raz et al., 1998). All these factors are known to contribute to the renal and glomerular growth in type 1 diabetes mellitus with the concomitant deterioration of the kidney function.

Type 2 diabetes mellitus - A continuous 24-hour infusion of native SST increased blood glucose levels due to the reduction of circulating insulin in type 2 diabetic patients (Christensen et al., 1978). Daily preprandial injection of octreotide in overweight type 2 diabetic patients reduced insulin and glucagon concentrations, without lowering hyperglycaemia (Davies et al., 1986). Noteworthy, in this study GH secretion was not affected, whereas free T4 was decreased and the frequency of bowel motions increased. SST-mediated changes in gut function may contribute to glucose control in that SST was reported to delay the intestinal glucose absorption, similar to antidiabetic actitivity of acarbose (Fery et al., 2005). In another study, low-doses of octreotide simultaneously given with insulin prevented the postprandial increase of blood glucose and plasma glucagon observed after injection of insulin alone (Giustina et al., 1991). In type 2 diabetic patients with chronic renal failure, but not in patients with normal kidney function, daily infusion of octreotide reduced plasma glucagon and C-peptide

concentration and decreased the insulin requirement (Di Mauro et al., 2001). Octreotide also reduced the rate of hepatic glucose production which could be due to suppression of glucagon secretion. The fall of increased C-peptide levels (marker of endogenous insulin secretion) could be possibly explained as a response of B-cells to decreased rate of hepatic glucose production and output. Reduction of insulin secretion could be a beneficial insulin-sparing effect, which could delay a progressive pancreatic B-cell exhaustion.

Expression of somatostatin receptors in the endocrine pancreas

Rodents

Expression of SST receptor isoforms, SSTR1, 2, 3 and 5, but not SSTR4, was observed in the rat pancreas using RT-PCR (Raulf et al., 1994). Multiple laboratories have used immunostaining to localize the various SSTRs to specific islet cells in rodents, with variable results, as summarized in Table 1. The discrepancies are likely related to the different affinity and species specificity of the antibodies used (Schindler et al., 1997; Kimura et al., 2001; Dournaud et al., 1996; Mitra et al., 1999; Ludvigsen et al., 2004). However, taken together these reports confirm the presence of SSTR2 on rat pancreatic A- and PP-cells, whereas B- and D-cells appear to express both SSTR 2 and SSTR5.

There is only one study available (Ludvigsen et al., 2005) describing the expression of SSTRs in the NOD mouse, which exhibit autoimmune-like type 1 diabetes with age (Bach 1994; Kikutani and Makino 1992). The pancreas of diabetic NOD mice is characterized by the reduced number of B-cells, whereas the volume density of A- and D-cells is increased (Gomez Dumm et al., 1995). Pancreatic islets in diabetic NOD and control ICR mice showed comparable expression levels of SSTR1 (Ludvigsen et al., 2005), while NOD mice with the most severe degree of insulitis had increased SSTR2 expression, whereas SSTR3-SSTR5 were increased in mice with a moderate severity of insulitis. In diabetic NOD mice with evidence of inflammatory cell invasion the expression of SSTR1 in pancreatic B-cells, SSTR1 and SSTR3 in A-cells and SSTR1 in D-cells were lower as compared to NOD mice without insulitis. Changes in expression of the SSTRs in inflamed islets indicate a potential role in the pathophysiology of autoimmune type 1 diabetes. NOD diabetes is characterized by the invasion of lymphocytes, which destroy pancreatic B-cells (Hayakawa et al., 1991). It was demonstrated that lymphocytes express SSTR2, and SSTR3, and that the expression pattern of these SSTRs depends upon the degree of lymphocyte maturation (Ferone et al., 2002). Thus, the positive correlation of SSTR2 overexpression with the severity of insulitis could correlate with the degree of the lymphocyte invasion. On the other hand it is possible that SSTRs are upregulated as a defense mechanism against hyperglucagonemia. Previous studies demonstrated a hyperplasia and hypertrophy of pancreatic D-cells in type 1 and type 2 diabetes (Rahier et al., 1983; Orci et al., 1976; Iki and Pour 2007; Gomez Dumm et al., 1995). Thus, both the increase in SST production as well as SSTR

expression on A-cells could provide a defense mechanism against hyperglucagonemia; however, experimental evidence supporting this hypothesis remains to be established.

Humans

A number of laboratories have used immunocytochemical methods to determine the pattern of SSTR expression in human islet cells (as summarized in Table 2), and similar to rodent studies the results vary, likely due to the different antibodies employed (Kumar et al., 1999; Papotti et al., 2002; Schindler et al., 1997; Schindler et al., 1998; Schulz et al., 1998; Portela-Gomes et al., 2000; Reubi et al., 1998; Gu and Schonbrunn 1997; Dournaud et al., 1996; Kimura et al., 2001; Taniyama et al., 2005). However, consistent across reports were the observations that human pancreatic A- and B-cells show a high expression of SSTR2, while striking inconsistencies remain with respect to cell-specific expression of SSTR1, SSTR3-SSTR5. Using SSTR specific agonists (Berk et al., 1999; Rohrer et al., 1998; Rohrer and Schaeffer 2000) to examine receptor specific effects on isolated human islet function Singh et al., (2007a) confirmed that activity of SSTR2 on B- and A-cell function and also observed B- and A-cells respond to SSTR1 and SSTR5. The question remains whether SST has the potential to autoregulate D-cell function, where some but not all reports using immunostaining show D-cells predominantly expression SSTR5.

Neuroendocrine tumors of the pancreas

A number of neuroendocrine islet cell tumors express a high density of SSTRs as determined by RT-PCR or immunohistochemistry (Table 3). Specifically, these very rare tumors can release neurohormones and biogenic amines (in up to 8% cases) that may determine the clinical symptoms.

Insulinomas are the most common pancreatic islet cell tumors, which can manifest as hypoglycaemia due to excessive production and hypersecretion of insulin. Insulinomas are in 90% of cases benign and solitary and in 99% they are located in the pancreas (Service et al., 1991). Collective evaluation of the SSTR expression analysis studies (Table 3) suggests insulinomas consistently express SSTR1 and SSTR2, while deSa et al., (2006) reported SSTR5 expression was positively correlated with tumor size and aggression. In that same study, the radioligand 125I-SST-14, bound to 13 out of 18 insulinomas as detected by autoradiography. In addition, using highly selective non-peptidal agonists in radioligand competition studies they found SSTR2 and SSTR5 binding sites in 72%, SSTR3 in 44%, SSTR1 in 44% and SSTR4 in 28% of insulinomas.

Glucagonoma (glucagon producing tumors) is the third most common endocrine-secreting islet cell tumor, which is in 70% of cases malignant. As summarized in Table 3, glucagonomas show a high expression of SSTR2 and lower expression of SSTR5, which is also the case for normal pancreatic A-cells. However, due to the very low incidence of glucagonomas, it is difficult to make a general statement regarding the typical expression pattern of SSTRs.

Gastrinomas (gastrin-producing tumors) account for up to 20% of pancreatic endocrine tumors. These tumors may cause gastric ulcer formation due to increased gastric acid secretion. SSTR2 (up to 100%) and SSTR5 (76 – 100%) are predominantly expressed in gastrinomas, which correlates well with the clinical responsiveness upon treatment with octreotide.

Somatostatinomas (somatostatin producing tumors), which are 90% malignant and PP-producing tumors are extremely rare. VIPomas are vasoactive intestinal polypeptide producing tumors that are frequently located in the endocrine islets. Due to very low number of both tumor entities it is difficult to make a general statement regarding SSTR expression. However, somatostatin agonists are useful to alleviate sysmptoms associated with tumor entity, which is malignant in 80-90% of cases (Jais et al., 1997; Kaltsas et al., 2001; Oda et al., 2002). Trying to summarize all these few cases published so far, SSTR5 seems to be predominantly expressed in somatostatinomas, whereas SSTR2 is predominantly expressed in VIPomas (Jais et al., 1997; Kaltsas et al., 2001; Oda et al., 2002), providing a molecular basis for the diagnostic and therapeutic targeting with radioactive octreotide.

Function of somatostatin receptors of the endocrine pancreas

Rodents

In vivo studies

Agonists

Several studies have emphasized the role of SSTR5 in regulating insulin secretion and SSTR2 in regulating glucagon secretion. In rats the SSTR5-selective DC-25-99 (also known as BIM-23052) decreased plasma insulin levels, whereas SSTR2- (NC 8-12) and SSTR3- (DC-25-20) selective agonists were inactive (Rossowski and Coy 1993). Two SSTR2-selective NC 8-12, DC-25-100 agonists more potently suppressed glucagon secretion in rats as compared to the SSTR5-selective agonist (DC-23-99) (Rossowski and Coy 1994). However, DC-25-99 was later identified as a pan-agonist at the SSTR1, SSTR2 and SSTR5 subtypes (Patel and Srikant 1994; Siehler et al., 1999) and the selectivity of other agonists has also been questioned in subsequent studies (Patel 1999; Patel 1997; Patel et al., 1995; Patel and Srikant 1994). For example the putative SSTR2-selective agonist NC 8-12, also binds to SSTR3 at nanomolar range and DC-25-100 to SSTR3 and SSTR4, as well as SSTR2 (Patel and Srikant 1994; Rossowski et al., 1994). The role of SSTR2 in regulating glucagon secretion was confirmed using a highly selective nonpeptidal agonist for SSTR2 (Yang et al., 1998), which potently reduced non-fasting glucagon secretion in non-diabetic, diabetic (ob/ob, db/db) mice and in fasted dogs (Strowski et al., 2006). Noteworthy, this was accompanied by a fall of plasma glucose concentrations. However in SSTR2-agonist treated dogs a moderate reduction of GH was observed, indicating that reduction of GH may contribute to the fall of blood glucose levels. The data obtained with agonists with moderate SSTR-selectivity indicate that SSTR2 regulates glucagon secretion, whereas SSTR5 inhibits insulin secretion.

Antagonists

The SSTR2-selective antagonist BIM-23627 has been previously demonstrated to reverse the SST-induced inhibition of growth hormone secretion from rodent primary pituitary cell cultures (Tulipano et al., 2002). In anesthetized adult rats and freely moving pups BIM-23627 increased plasma glucagon and blood glucose concentration after 20 min (Tulipano et al., 2002). Insulin levels were slightly increased at the highest dose of BIM-23627. Of note, BIM-23627 displays a moderate selectivity for SSTR2 compared to SSTR5 (IC50 values: SSTR2: 6.4 nM vs. SSTR5: 86.5 nM). DC-41-33 is an SSTR2-specific antagonist having 9-21 times lower affinity for SSTR3 and SSTR5 (Hocart et al., 1999; Rossowski et al., 1998). In perifused islets DC-41-33 more potently enhanced the maximal and the arginine-stimulated second phase of glucagon secretion, as compared to its effects on insulin secretion (Cejvan et al., 2003). While the effects on glucagon are clearly SSTR2-dependent, the moderate stimulation of insulin secretion suggests that SSTR2 may be involved in regulating insulin secretion. An alternative explanation is based upon the fact that glucagon can stimulate insulin secretion. As arginine is able to stimulate insulin and glucagon secretion, the inhibition of insulin secretion by DC-41-33 could be secondary to an arginine-increase of glucagon secretion. However, DC-41-33 could interfere with pancreatic B-cells due to limited selectivity, so testing of DC-41-33 on isolated and purified B-cells or permanent pancreatic B-cell cultures would provide an explanation for this phenomenon. Thus, the results obtained with two different SSTR2-antagonists support the notion that SSTR2 inhibits glucagon secretion in rodents.

In vitro studies

Agonists

A very recent study (Ludvigsen et al., 2007) evaluated the effects of the following agonists on insulin and glucagon secretion from isolated rat pancreatic islets: SOM230 (panagonist), SSTR1-selective (BIM-23926 IC50 of 3.6 nM for SSTR1 and > 800 nM for other SSTRs (Zatelli et al., 2002)), SSTR2-selective (BIM-23120, IC50 of 0.34 nM for SSTR2, and over 200 nM for other SSTRs (Zatelli et al., 2001; Zatelli et al., 2002; Shimon et al., 1997b; Shimon et al., 1997a; Saveanu et al., 2001)) and SSTR5-selective (BIM-23206, IC50 of 2.4 nM for SSTR5 and more than 15 nM for other 4 SSTRs). SOM230 was a superior inhibitor of insulin secretion as compared to octreotide or SST-14 after a longer incubation period of 48 hours. Importantly, the insulino- or glucagonostatic effects were observed only if the islets were exposed to a combination of two agonists (SSTR2 together with SSTR5 or SSTR1 together with the SSTR2). In contrast SSTR1, SSTR2 or SSTR5-selective agonists alone were ineffective. While the insulinostatic (SSTR2 and SSTR5) and glucagonostatic (SSTR1 and SSTR2) roles of SSTRs indicated in previous studies on murine islets were confirmed, these results shed new insights into the regulation the endocrine pancreas activity through agonist-dependent heterodimerization. Using cell-based expression studies it has been previously demonstrated that SSTR1 and SSTR5 exist as monomers in the basal state. However, in the presence of SST agonists, SSTR1 and SSTR5 are able to form heterodimers with each other (Rocheville et al., 2000; Patel et al., 2002). Since

both B- and A-cells of the endocrine express multiple SSTRs. The receptors could be recruited to form homo- or heterodimers, depending on the absence or presence of the particular agonist employed, thus providing a potential explanation for the discrepancies between studies with respect to which SSTR regulates insulin and glucagon secretion.

For instance an up-regulation of SSTR1 membrane expression, through a process of receptor recruitment from a pre-existing cytoplasmic pool to the plasma membrane (Hukovic et al., 1999), is observed if cells are exposed to SST or even to octreotide, which does not bind to SSTR1. However, in a heterologous expression system (SSTR1 and SSTR5-transfected cells) octreotide can bind to SSTR5, leading to agonist-induced heterodimerization of SSTR5 with SSTR1. Increased SSTR1 expression can cause more profound biological effects upon exposure of islets to an agonist. It is possible that other SSTR-multireceptor agonists (e.g. SOM230) are able to induce hetereodimerization of SSTRs, rendering even receptors more active.

A similar phenomenon was recently reported in MCF-7 human breast cells that express native SSTRs. A recruitment of SSTR1 to the plasma membrane translated into enhanced biological activity following exposure to octreotide.

The heterodimerization probably also exists between SSTR1 and SSTR2, since octreotide has by far the highest affinity to SSTR2. However, neither SSTR1/SSTR2 not SSTR2/SSTR5 heterodimerization have been investigated to date.

Antagonists

A study with an SSTR2 antagonist DC-41-33 potentiated the rise of arginine-stimulated glucagon secretion at low glucose and antagonized SST-dependent inhibition of glucagon secretion in rat pancreatic islets confirmed the role of SSTR2 as an inhibitor of glucagon secretion (Cejvan et al., 2003). The effects of DC-41-33 on insulin secretion were much less potent. Again, these data support the major role of SSTR2 in regulating glucagon secretion, and indicate a minor role of SSTR2 in regulating insulin secretion.

Knock out mouse models

In vivo studies

The insulinostatic role of SSTR5 was confirmed by Wang et al (Wang et al., 2005) using SSTR5 knockout mice. Specifically they reported that SSTR5-deficient mice with age display an increase in basal and stimulated insulin secretion and decreased glucose levels (Wang et al., 2005). High-fat diet induced obesity in younger mice with the deletion of the SSTR5-gene resulted in less prominent glucose intolerance and lower basal insulin concentration, as compared to control mice (Strowski et al., 2003). While the results of the study on lean animals fit very well with the inhibitory function of SSTR5 on insulin secretion, the metabolic changes in SSTR5-/- mice with diet-induced obesity are unexpected. Underlying mechanisms, could involve changes of insulin sensitivity, which was also reported in SSTR1-/- mice. A candidate peptide that could play a role at improving insulin sensitivity is leptin, which expression in adipocytes of SSTR5 knockout mice increased.

Deletion of SSTR1 gene in mice was also reported to result in age-dependent alterations in the kinetic of insulin release and altered glucose homeostasis (Wang et al., 2006). Younger SSTR1-deficient mice had

increased fasting glucose, decreased insulin concentration and decreased insulin sensitivity. Glucose-stimulated insulin secretion was initially lower and later excessive, as compared to normal mice. Older SSTR1-/- mice had increased fasting glucose levels, decreased basal and increased glucose-stimulated insulin secretion (Wang et al., 2006). These data indicate that SSTR1 inhibits insulin secretion, modulates the kinetics of insulin secretion and possibly influences insulin sensitivity. The delay of insulin secretion in SSTR1-deficient mice may account for increased glucose levels in younger SSTR1-deficient mice. A sufficient explanation for these unexpected and somehow contradictory results in older mice has not been provided by the authors and requires further investigation of these animals with respect to the insulin sensitivity and peripheral glucose utilization. It is possible that SSTR1 plays a role in the development and maturation of the endocrine islet cells; however data supporting this hypothesis are still not available.

The insulinostatic role of both SSTR1 and SSTR5 was confirmed in SSTR1/SSTR5 double knockout mice, which showed increased insulin secretion in response to challenge with glucose (Wang et al., 2004). However, insufficient information regarding the strain, age or sex of the mice used in the SSTR1/SSTR5 knockout study, makes accurate comparison with other studies difficult. Moreover, the consequences of simultaneous deletion of SSTR1/SSTR5 on glucagon secretion were not characterized, leaving speculations on whether changes of glucagon secretion contribute to changes of glycemia.

Recently, the role of SSTR2 in regulating glucagon secretion has been strengthened by the results of two separate in vivo studies utilizing lean and obese SSTR2-deficient mice (Strowski et al., 2006; Singh et al., 2007b). Specifically, the deterioration of glycemic control in SSTR2-deficient mice fed high-fat diet, suggests a potential novel therapeutic opportunity to alleviate hyperglycemia in diabetes. It was demonstrated for the first time that the deletion of SSTR2 increases non-fasting glucagon secretion, resulting in lower glycogen storage in the liver. While both studies provide strong evidence for the glucagonostatic activity of SSTR2 in mice, there are several questions arising based on the analysis of the phenotypic alterations observed in these animals. How, if at all, are the SSTR2-deficient animals with low hepatic glycogen content protected against hypoglycaemia? Could alterations in GH output also impact glucose homeostasis in SSTR2-/- mice? Finally, based on human studies, it appears that there are considerable species differences regarding the SSTR2 function and expression, which suggest caution in a direct extrapolation of a phenomenon observed in rodent studies on humans.

In vitro studies

Using pancreatic islets isolated from mice with SSTR2-deletion (Zheng et al., 1997), SST and two different non-peptidal SSTR2-selective agonists were unable to inhibit glucagon secretion (Strowski et al., 2000; Strowski et al., 2006). These observations coupled with the inability of other SSTR-selective agonists to influence glucagon secretion (Berk et al., 1999; Rohrer et al., 1998; Rohrer and Schaeffer 2000) favours the glucagonostatic role of SSTR2 in mice. A minor reduction of glucagon secretion by an SSTR5-selective agonist (approx. 20%) in this study (Strowski et al., 2000) could be explained by the agonist's lower receptor subtype selectivity (10-100-fold). In particular, the interaction with an SSTR1 could be possible, due to only 10-fold difference in selectivity (Rohrer et al., 1998; Rohrer and Schaeffer 2000). This hypothesis could also explain the residual inhibition of glucagon secretion from SSTR2-deficient islets by SST-28 (Strowski et al., 2000). This study also demonstrated that the deletion of

SSTR2 leads to the loss of moderate insulinostatic activity of the SSTR2-agonist, suggesting that at higher concentrations an SSTR2-agonist could interfere with other SSTRs (at 100 nM).

The SSTR-multireceptor theory as regulators of murine insulin secretion was confirmed using islets lacking the SSTR5 gene (Strowski et al., 2003). In these SSTR5-deficient islets the insulinostatic activities of both SST-28 and a SSTR5-selective agonist were markedly attenuated, but not completely lost. Importantly, a SSTR2-selective agonist showed a moderate activity on insulin secretion, regardless of SSTR5 status. Thus, at least SSTR2 and SSTR5 plays a role at inhibiting insulin secretion, and the results of a study on mice with the simultaneous deletion of both SSTR1 and SSTR5 emphasize the additional role of SSTR1 (Wang et al., 2004). Using SSTR1/SSTR5-deficient islets it was demonstrated that octreotide, SST-28 and SST-14 failed to inhibit glucose-stimulated insulin secretion.

The results of these studies indicate that SSTR1, SSTR2 and SSTR5 regulate murine insulin secretion. While the residual activity of the SSTR5-selective agonist (Berk et al., 1999; Rohrer et al., 1998; Rohrer and Schaeffer 2000) on insulin secretion from SSTR5-deficient islets (Strowski et al., 2003) could be explained by an interaction with the SSTR1 (only 10-fold selectivity). Collectively, there are several important findings originating from the studies mentioned above that could be possibly explained by the ability of SSTRs to interact with each other.

Thus, beside SSTR5 there are other SSTRs (most likely SSTR1 due to a low selectivity of SSTR5-agonist and SSTR2), which could mediate the insulinostatic effects of SST. Another possibility is a compensatory up-regulation of SSTRs in mice with a homozygous deletion of the SSTR5 gene, however this issue has not been investigated. Lastly, the disruption of SSTR1/SSTR5 could have a profound impact on receptor heterodimerization, inactivating agonists that under normal conditions could (at least slightly) reduce insulin secretion (e. g. octreotide). This was the case for octreotide, which despite the presence of SSTR2 on pancreatic B-cells was unable to inhibit insulin secretion from SSTR1/SSTR5-defieicnt islets. However, this study did not investigate the changes of SSTR2 expression, thus alternate hypotheses are possible.

Ex vivo studies

Using perfused pancreata obtained from mice with the deletion of SSTR1, SSTR5 or both SSTR1 and SSTR5 it was demonstrated that SSTR1 and SSTR5 are able to reduce the first and/or second phase of glucose-stimulated insulin secretion (Wang et al., 2006; Tirone et al., 2003; Wang et al., 2004). However, the deletion of SSTR1 or SSTR5 in glucose-intolerant sulfonylurea receptor 1 knock out (SUR1-/-) mice (Seghers et al., 2000) failed to restore the impaired first and the second phase of insulin secretion in islets derived from SUR1-/- mice (Norman et al., 2002). Conversely, an SSTR1/SSTR5-selective antagonist would presumably restore impaired first and second phases of insulin secretion, rendering this an attractive therapeutic target for type 2 diabetes. However, in the current model, the deletion of SSTR5 did not rescue the SUR1-/- phenotype. An explanation was not provided in this study. Assuming that SSTR5 inhibits SST secretion, and that D-cells share many similarities with B-cells, it is not possible to predict whether SST secretion would increase or decrease. The deletion of the inhibitory SSTR5 would increase SST secretion; however lack of SUR1 would result in the lower secretion activity of D-cells. However, this question was not asked in this study and no data were provided regarding the secretion of glucagon. In summary, the results of these studies indicate that SSTR1 and SSTR5 inhibit murine insulin secretion.

Humans

In contrast to rodents, fewer studies are available on the role of individual SSTRs in regulating the secretion of glucagon and insulin from the human endocrine pancreas. To date, the best characterized SSTRs in humans are SSTR2 and SSTR5, which is probably due to the availability of agonists that preferentially interact with these receptor subtypes, in addition to the high expression levels of these receptor subtypes in the pancreas.

In vitro studies

Similar to results in rodent models, Zambre et al (1999) reported SSTR5 agonists of moderate to high selectivity for SSTR5 (BIM-23268 and BIM-2313 inhibited glucose-stimulated insulin secretion, while SSTR2 agonists were ineffective in this regard. However, three different studies (Brunicardi et al., 2003; Moldovan et al., 1995; Atiya et al., 1997) using perfused pancreas revealed octreotide and SSTR2-selective agent (NC-8-12) were the most potent inhibitors of insulin secretion. Since, SSTR5- (DC-32-92) and SSTR3-selective (DC-25-12) agonists only minimally inhibited insulin release at high concentrations. These data indicate that the SSTR2 is the major receptor subtype in humans mediating the inhibition of insulin secretion by SST. The role of SSTR2 as the primary transducer of SST-mediated insulin release is further supported by a recent study (Singh et al., 2007a) reporting that a nonpeptidal SSTR2-selective agonist was by far the most potent inhibitor of stimulated insulin secretion, followed by SSTR5 and SSTR1-selective agonists. In addition, the same highly SSTR2-selective nonpeptidal agonist potently inhibited glucagon secretion followed by SSTR1- and SSTR5-selective agonists. SSTR2-agonist dependent inhibition of both insulin and glucagon secretion was blocked by the SSTR2-selective antagonist DC-41-33 (PRL-2903), further strengthening the primary inhibitory role of SSTR2 on A- and B-cell secretion.

When interpreting these in vitro human data and also the results of animal studies utilizing the non-peptidal SSTR5 agonist developed by Merck (Rohrer et al., 1998) it is important to emphasize that the SSTR5 agonist displays only a 10-fold selectivity for human SSTR5 vs. SSTR1 and approximately 100-fold or higher as compared to other SSTRs (Rohrer et al., 1998). Therefore, it is impossible to rule out the interaction of SSTR5-selective agonist with the remaining SSTRs. Silencing of individual SSTR expression by using receptor specific siRNA could be potentially helpful to resolve this issue.

In vivo studies

The knowledge regarding the role SSTRs in regulation of pancreatic function in vivo bases on observations derived from clinical studies in which SST agonists are used to treat GH hypersecretion in acromegaly. Standard medical treatment includes octreotide, which acts predominantly via SSTR2 and more recently a panagonist, the peptidomimetic SOM230 which has a 30-40-fold higher binding affinity to SSTR1 and SSTR5 and a more potent long lasting effect on suppression of GH and IGF-I, as compared to octreotide (Bruns et al., 2002; Weckbecker et al., 2002). In humans, both octreotide and SOM230 (transiently) elevated blood glucose levels, however in contrast to octreotide, SOM230 did not inhibit insulin secretion (van der Hoek J. et al., 2004). The inhibition of insulin secretion in humans by octreotide and the lack thereof in SOM230-treated patients further supports the bulk of in vitro studies indicating insulin secretion is regulated via SSTR2. This is in contrast to the effects of octreotide and SOM230 in rodents where both are able to inhibit insulin secretion (Bruns et al., 2002). These species differences may be directly related to the fact that human B-cells show a high expression of SSTR2

(Table 3), whereas in rodents SSTR5 seems to be the main B-cell receptor subtype (Table 1), However, since SOM230 has effects on multiple systems in vivo (including GH) which could indirectly regulate pancreatic function, we await the results of studies examining the direct effects of SOM230 in the perfused human pancreas or isolated pancreatic islets.

Concluding remarks

Despite species differences in terms of SSTR structures, sequence homology and expression patterns, it is becoming clear that in humans three SSTRs (SSTR1, SSTR2 and SSTR5) are playing roles in inhibiting insulin and glucagon secretion in humans and insulin secretion in rodents. Alternatively, SSTR2 (but probably not SSTR1 and SSTR5) seems to be important inhibitors of glucagon secretion in rodents. While in rodents the SSTR5 subtype is a more potent inhibitor of insulin secretion than SSTR2, the reciprocal is true for the regulation of glucagon secretion. In humans, SSTR2 appears to be a universal inhibitor of insulin and glucagon secretion, which clearly differs from rodent models. However, knowing that SSTRs are able to heterodimerize, depending upon SST agonists, and through recent introduction of pan-selective agonists, our understanding of the functional relevance of individual SSTRs is undergoing revision. A more complex interaction seems to be induced upon the exposure to panagonists. The challenge is going to be to investigate this issue in better detail, to find a potential implication of the agonists in therapy of diseases induced by pathological secretion of pancreatic and extrapancreatic cells and tissues.

References

Atiya, A. W., Moldovan, S., Adrian, T. E., Coy, D., Walsh, J., Brunicardi, F. C., 1997. Intraislet Somatostatin Inhibits Insulin (Via a Subtype-2 Somatostatin Receptor) But Not Islet Amyloid Polypeptide Secretion in the Isolated Perfused Human Pancreas. J. Gastrointest. Surg. 1, 251-256.

Bach, J. F., 1994. Insulin-dependent diabetes mellitus as an autoimmune disease. Endocr. Rev. 15, 516-542.

Baskin, D. G., Ensinck, J. W., 1984. Somatostatin in epithelial cells of intestinal mucosa is present primarily as somatostatin 28. Peptides 5, 615-621.

Berk, S. C., Rohrer, S. P., Degrado, S. J., Birzin, E. T., Mosley, R. T., Hutchins, S. M., Pasternak, A., Schaeffer, J. M., Underwood, D. J., Chapman, K. T., 1999. A combinatorial approach toward the discovery of non-peptide, subtype-selective somatostatin receptor ligands. J. Comb. Chem. 1, 388-396.

Binimelis, J., Webb, S. M., Mones, J., Serrano, J., Casamitjana, R., Elena, M., Peinado, M. A., Vilardell, F., De Leiva, A., 1987. Circulating immunoreactive somatostatin in gastrointestinal diseases. Decrease after vagotomy and enhancement in active ulcerative colitis, irritable bowel syndrome, and duodenal ulcer. Scand. J. Gastroenterol. 22, 931-937.

Brand, C. L., Rolin, B., Jorgensen, P. N., Svendsen, I., Kristensen, J. S., Holst, J. J., 1994. Immunoneutralization of endogenous glucagon with monoclonal glucagon antibody normalizes hyperglycaemia in moderately streptozotocin-diabetic rats. Diabetologia 37, 985-993.

Brazeau, P., Vale, W., Burgus, R., Ling, N., Butcher, M., Rivier, J., Guillemin, R., 1973. Hypothalamic polypeptide that inhibits the secretion of immunoreactive pituitary growth hormone. Science 179, 77-79.

Brunicardi, F. C., Atiya, A., Moldovan, S., Lee, T. C., Fagan, S. P., Kleinman, R. M., Adrian, T. E., Coy, D. H., Walsh, J. H., Fisher, W. E., 2003. Activation of somatostatin receptor subtype 2 inhibits insulin secretion in the isolated perfused human pancreas. Pancreas 27, e84-e89.

Brunicardi, F. C., Kleinman, R., Moldovan, S., Nguyen, T. H., Watt, P. C., Walsh, J., Gingerich, R., 2001. Immunoneutralization of somatostatin, insulin, and glucagon causes alterations in islet cell secretion in the isolated perfused human pancreas. Pancreas 23, 302-308.

Bruns, C., Lewis, I., Briner, U., Meno-Tetang, G., Weckbecker, G., 2002. SOM230: a novel somatostatin peptidomimetic with broad somatotropin release inhibiting factor (SRIF) receptor binding and a unique antisecretory profile. Eur. J. Endocrinol. 146, 707-716.

Burgus, R., Ling, N., Butcher, M., Guillemin, R., 1973. Primary structure of somatostatin, a hypothalamic peptide that inhibits the secretion of pituitary growth hormone. Proc. Natl. Acad. Sci. U. S. A 70, 684-688.

Cabrera, O., Berman, D. M., Kenyon, N. S., Ricordi, C., Berggren, P. O., Caicedo, A., 2006. The unique cytoarchitecture of human pancreatic islets has implications for islet cell function. Proc. Natl. Acad. Sci. U. S. A 103, 2334-2339.

Cejvan, K., Coy, D. H., Efendic, S., 2003. Intra-islet somatostatin regulates glucagon release via type 2 somatostatin receptors in rats. Diabetes 52, 1176-1181.

Christensen, S. E., Hansen, A. P., Orskov, H., Lundbaek, K., 1978. Twenty-four-hour somatostatin infusions in normals, juvenile diabetics, and maturity-onset diabetics. Metabolism 27, 1427-1431.

D'Alessio, D. A., Ensinck, J. W., 1990. Fasting and postprandial concentrations of somatostatin-28 and somatostatin-14 in type II diabetes in men. Diabetes 39, 1198-1202.

D'Alessio, D. A., Sieber, C., Beglinger, C., Ensinck, J. W., 1989. A physiologic role for somatostatin 28 as a regulator of insulin secretion. J. Clin. Invest 84, 857-862.

Daunt, M., Dale, O., Smith, P. A., 2006. Somatostatin inhibits oxidative respiration in pancreatic beta-cells. Endocrinology 147, 1527-1535.

Davies, R. R., Miller, M., Turner, S. J., Watson, M., McGill, A., Orskov, H., Alberti, K. G., Johnston, D. G., 1986. Effects of somatostatin analogue SMS 201-995 in non-insulin-dependent diabetes. Clin. Endocrinol. (Oxf) 25, 739-747.

de Laszlo, S. E., Hacker, C., Li, B., Kim, D., MacCoss, M., Mantlo, N., Pivnichny, J. V., Colwell, L., Koch, G. E., Cascieri, M. A., Hagmann, W. K., 1999. Potent, orally absorbed glucagon receptor antagonists. Bioorg. Med. Chem. Lett. 9, 641-646.

Di Mauro, M., Papalia, G., Le Moli, R., Nativo, B., Nicoletti, F., Lunetta, M., 2001. Effect of octreotide on insulin requirement, hepatic glucose production, growth hormone, glucagon and c-peptide levels in type 2 diabetic patients with chronic renal failure or normal renal function. Diabetes Res. Clin. Pract. 51, 45-50.

Dinneen, S., Alzaid, A., Turk, D., Rizza, R., 1995. Failure of glucagon suppression contributes to postprandial hyperglycaemia in IDDM. Diabetologia 38, 337-343.

Dournaud, P., Gu, Y. Z., Schonbrunn, A., Mazella, J., Tannenbaum, G. S., Beaudet, A., 1996. Localization of the somatostatin receptor SST2A in rat brain using a specific anti-peptide antibody. J. Neurosci. 16, 4468-4478.

Efendic, S., Lins, P. E., Luft, R., 1978. Somatostatin and insulin secretion. Metabolism 27, 1275-1281.

Fehmann, H. C., Strowski, M., Goke, B., 1995. Functional characterization of somatostatin receptors expressed on hamster glucagonoma cells. Am. J. Physiol 268, E40-E47.

Ferone, D., Pivonello, R., van Hagen, P. M., Dalm, V. A., Lichtenauer-Kaligis, E. G., Waaijers, M., van Koetsveld, P. M., Mooy, D. M., Colao, A., Minuto, F., Lamberts, S. W., Hofland, L. J., 2002. Quantitative and functional expression of somatostatin receptor subtypes in human thymocytes. Am. J. Physiol Endocrinol. Metab 283, E1056-E1066.

Fery, F., Tappy, L., Schneiter, P., Deviere, J., Balasse, E. O., 2005. Effect of somatostatin on duodenal glucose absorption in man. J. Clin. Endocrinol. Metab 90, 4163-4169.

Gelling, R. W., Du, X. Q., Dichmann, D. S., Romer, J., Huang, H., Cui, L., Obici, S., Tang, B., Holst, J. J., Fledelius, C., Johansen, P. B., Rossetti, L., Jelicks, L. A., Serup, P., Nishimura, E., Charron, M. J., 2003. Lower blood glucose, hyperglucagonemia, and pancreatic alpha cell hyperplasia in glucagon receptor knockout mice. Proc. Natl. Acad. Sci. U. S. A 100, 1438-1443.

Gerich, J. E., Lorenzi, M., Schneider, V., Karam, J. H., Rivier, J., Guillemin, R., Forsham, P. H., 1974. Effects of somatostatin on plasma glucose and glucagon levels in human diabetes mellitus. Pathophysiologic and therapeutic implications. N. Engl. J. Med. 291, 544-547.

Gerich, J. E., Schultz, T. A., Lewis, S. B., Karam, J. H., 1977. Clinical evaluation of somatostatin as a potential ajunct to insulin in the management of diabetes mellitus. Diabetologia 13, 537-544.

Giustina, A., Girelli, A., Buffoli, M. G., Cimino, A., Legati, F., Valentini, U., Giustina, G., 1991. Low-dose octreotide is able to cause a maximal inhibition of the glycemic responses to a mixed meal in obese type 2 diabetic patients treated with insulin. Diabetes Res. Clin. Pract. 14, 47-54.

Gomez Dumm, C. L., Console, G. M., Luna, G. C., Dardenne, M., Goya, R. G., 1995. Quantitative immunohistochemical changes in the endocrine pancreas of nonobese diabetic (NOD) mice. Pancreas 11, 396-401.

Grill, V., Efendic, S., 1983. Loss of a priming effect of glucose on A and D cell secretion in perfused pancreases from alloxan-diabetic rats: role of insulin and alloxan. Diabetologia 24, 47-51.

Gromada, J., Hoy, M., Buschard, K., Salehi, A., Rorsman, P., 2001. Somatostatin inhibits exocytosis in rat pancreatic alpha-cells by G(i2)-dependent activation of calcineurin and depriming of secretory granules. J. Physiol 535, 519-532.

Gu, Y. Z., Schonbrunn, A., 1997. Coupling specificity between somatostatin receptor sst2A and G proteins: isolation of the receptor-G protein complex with a receptor antibody. Mol. Endocrinol. 11, 527-537.

Gutniak, M., Grill, V., Efendic, S., 1986. Effects of insulin on fasting and meal-stimulated somatostatin-like immunoreactivity in noninsulin-dependent diabetes mellitus: evidence for more than one mechanism of action. J. Clin. Endocrinol. Metab 62, 77-83.

Gutniak, M., Grill, V., Roovete, A., Efendic, S., 1989. Impaired somatostatin response to orally administered glucose in type II diabetes entails both somatostatin-28 and -14 and is associated with deranged metabolic control. Acta Endocrinol. (Copenh) 121, 322-326.

Hansen, I., Tsalikian, E., Beaufrere, B., Gerich, J., Haymond, M., Rizza, R., 1986. Insulin resistance in acromegaly: defects in both hepatic and extrahepatic insulin action. Am. J. Physiol 250, E269-E273.

Hayakawa, M., Yokono, K., Nagata, M., Hatamori, N., Ogawa, W., Miki, A., Mizoguti, H., Baba, S., 1991. Morphological analysis of selective destruction of pancreatic beta-cells by cytotoxic T lymphocytes in NOD mice. Diabetes 40, 1210-1217.

Hermansen, K., 1980. Secretion of somatostatin from the normal and diabetic pancreas. Studies in vitro. Diabetologia 19, 492-504.

Hermansen, K., 1981. Characterisation of the abnormal pancreatic D and A cell function in streptozotocin diabetic dogs: studies with D-glyceraldehyde, dihydroxyacetone, D-mannoheptulose, D-glucose, and L-arginine. Diabetologia 21, 489-494.

Hocart, S. J., Jain, R., Murphy, W. A., Taylor, J. E., Coy, D. H., 1999. Highly potent cyclic disulfide antagonists of somatostatin. J. Med. Chem. 42, 1863-1871.

Hukovic, N., Rocheville, M., Kumar, U., Sasi, R., Khare, S., Patel, Y.C., 1999. Agonist-dependent up-regulation of human somatostatin receptor type 1 requires molecular signals in the cytoplasmic C-tail. J. Biol Chem. 274, 24550-2458.

Iki, K., Pour, P. M., 2007. Distribution of pancreatic endocrine cells including IAPP-expressing cells in non-diabetic and type 2 diabetic cases. J. Histochem. Cytochem. 55, 111-118.

Ipp, E., Dobbs, R. E., Arimura, A., Vale, W., Harris, V., Unger, R. H., 1977. Release of immunoreactive somatostatin from the pancreas in response to glucose, amino acids, pancreozymin-cholecystokinin, and tolbutamide. J. Clin. Invest 60, 760-765.

Jais P, Terris B, Ruszniewski P, LeRomancer M, Reyl-Desmars F, Vissuzaine C, Cadiot G, Mignon M, Lewin MJ 1997 Somatostatin receptor subtype gene expression in human endocrine gastroentero-pancreatic tumours. Eur J Clin Invest 27:639-644

Kadowaki, S., Taminato, T., Chiba, T., Goto, Y., Nozawa, M., Seino, Y., Matsukura, S., Fujita, T., 1980. Somatostatin release from the isolated, perfused diabetic rat pancreas: inverse relationship between pancreatic somatostatin and insulin. Diabetes 29, 960-963.

Kaltsas G, Mukherjee JJ, Plowman PN, Grossman AB 2001 The role of chemotherapy in the nonsurgical management of malignant neuroendocrine tumours. Clin Endocrinol (Oxf) 55:575-587

Kanatsuka, A., Makino, H., Matsushima, Y., Osegawa, M., Kasanuki, J., Miyahira, M., Yamamoto, M., Kumagai, A., 1981. Effect of glucose on somatostatin secretion from isolated pancreatic islets of normal and streptozotocin-diabetic rats. Endocrinology 109, 652-657.

Kendall, D. M., Poitout, V., Olson, L. K., Sorenson, R. L., Robertson, R. P., 1995. Somatostatin coordinately regulates glucagon gene expression and exocytosis in HIT-T15 cells. J. Clin. Invest 96, 2496-2502.

Kikutani, H., Makino, S., 1992. The murine autoimmune diabetes model: NOD and related strains. Adv. Immunol. 51, 285-322.

Kimura, N., Schindler, M., Kasai, N., Kimura, I., 2001. Immunohistochemical localization of somatostatin receptor type 2A in rat and human tissues. Endocr. J. 48, 95-102.

Klaff, L. J., Taborsky, G. J., Jr., 1987. Pancreatic somatostatin is a mediator of glucagon inhibition by hyperglycemia. Diabetes 36, 592-596.

Kleinman, R., Gingerich, R., Ohning, G., Wong, H., Olthoff, K., Walsh, J., Brunicardi, F. C., 1995. The influence of somatostatin on glucagon and pancreatic polypeptide secretion in the isolated perfused human pancreas. Int. J. Pancreatol. 18, 51-57.

Kleinman, R., Ohning, G., Wong, H., Watt, P., Walsh, J., Brunicardi, F. C., 1994. Regulatory role of intraislet somatostatin on insulin secretion in the isolated perfused human pancreas. Pancreas 9, 172-178.

Koerker, D. J., Ruch, W., Chideckel, E., Palmer, J., Goodner, C. J., Ensinck, J., Gale, C. C., 1974. Somatostatin: hypothalamic inhibitor of the endocrine pancreas. Science 184, 482-484.

Kumar, U., Sasi, R., Suresh, S., Patel, A., Thangaraju, M., Metrakos, P., Patel, S. C., Patel, Y. C., 1999. Subtype-selective expression of the five somatostatin receptors (hSSTR1-5) in human pancreatic islet cells: a quantitative double-label immunohistochemical analysis. Diabetes 48, 77-85.

Liang, Y., Osborne, M. C., Monia, B. P., Bhanot, S., Gaarde, W. A., Reed, C., She, P., Jetton, T. L., Demarest, K. T., 2004. Reduction in glucagon receptor expression by an antisense oligonucleotide ameliorates diabetic syndrome in db/db mice. Diabetes 53, 410-417.

Liljenquist, J. E., Bloomgarden, Z. T., Cherrington, A. D., Perry, J. M., Rabin, D., 1979. Possible mechanism by which somatostatin-induced glucagon suppression improves glucose tolerance during insulinopaenia in man. Diabetologia 17, 139-143.

Ludvigsen, E., Olsson, R., Stridsberg, M., Janson, E. T., Sandler, S., 2004. Expression and distribution of somatostatin receptor subtypes in the pancreatic islets of mice and rats. J. Histochem. Cytochem. 52, 391-400.

Ludvigsen, E., Stridsberg, M., Janson, E. T., Sandler, S., 2005. Expression of somatostatin receptor subtypes 1-5 in pancreatic islets of normoglycaemic and diabetic NOD mice. Eur. J. Endocrinol. 153, 445-454.

Ludvigsen, E., Stridsberg, M., Taylor, J. E., Culler, M. D., Oberg, K., Janson, E. T., Sandler, S., 2007. Regulation of insulin and glucagon secretion from rat pancreatic islets in vitro by somatostatin analogues. Regul. Pept. 138, 1-9.

Madsen, P., Ling, A., Plewe, M., Sams, C. K., Knudsen, L. B., Sidelmann, U. G., Ynddal, L., Brand, C. L., Andersen, B., Murphy, D., Teng, M., Truesdale, L., Kiel, D., May, J., Kuki, A., Shi, S., Johnson, M. D., Teston, K. A., Feng, J., Lakis, J., Anderes, K., Gregor, V., Lau, J., 2002. Optimization of alkylidene hydrazide based human glucagon receptor antagonists. Discovery of the highly potent and orally available 3-cyano-4-hydroxybenzoic acid [1-(2,3,5,6-tetramethylbenzyl)-1H-indol-4-ylmethylene]hydrazide. J. Med. Chem. 45, 5755-5775.

Makino, H., Matsushima, Y., Kanatsuka, A., Yamamoto, M., Kumagai, A., Nishimura, M., 1979. Changes in pancreatic somatostatin content in spontaneously diabetic mice, as determined by radioimmunoassay and immunohistochemical methods. Endocrinology 104, 243-247.

Mandarino, L., Stenner, D., Blanchard, W., Nissen, S., Gerich, J., Ling, N., Brazeau, P., Bohlen, P., Esch, F., Guillemin, R., 1981. Selective effects of somatostatin-14, -25 and -28 on in vitro insulin and glucagon secretion. Nature 291, 76-77.

Mitra, S. W., Mezey, E., Hunyady, B., Chamberlain, L., Hayes, E., Foor, F., Wang, Y., Schonbrunn, A., Schaeffer, J. M., 1999. Colocalization of somatostatin receptor sst5 and insulin in rat pancreatic beta-cells. Endocrinology 140, 3790-3796.

Moldovan, S., Atiya, A., Adrian, T. E., Kleinman, R. M., Lloyd, K., Olthoff, K., Imagawa, D., Shevlin, L., Coy, D., Walsh, J., ., 1995. Somatostatin inhibits B-cell secretion via a subtype-2 somatostatin receptor in the isolated perfused human pancreas. J. Surg. Res. 59, 85-90.

Moller, L. N., Stidsen, C. E., Hartmann, B., Holst, J. J., 2003. Somatostatin receptors. Biochim. Biophys. Acta 1616, 1-84.

Muroyama, A., Uehara, S., Yatsushiro, S., Echigo, N., Morimoto, R., Morita, M., Hayashi, M., Yamamoto, A., Koh, D. S., Moriyama, Y., 2004. A novel variant of ionotropic glutamate receptor regulates somatostatin secretion from delta-cells of islets of Langerhans. Diabetes 53, 1743-1753.

Nilsson, T., Arkhammar, P., Rorsman, P., Berggren, P. O., 1989. Suppression of insulin release by galanin and somatostatin is mediated by a G-protein. An effect involving repolarization and reduction in cytoplasmic free Ca2+ concentration. J. Biol. Chem. 264, 973-980.

Noe, B. D., 1981. Synthesis of one form of pancreatic islet somatostatin predominates. J. Biol. Chem. 256, 9397-9400.

Norman, M., Moldovan, S., Seghers, V., Wang, X. P., Demayo, F. J., Brunicardi, F. C., 2002. Sulfonylurea receptor knockout causes glucose intolerance in mice that is not alleviated by concomitant somatostatin subtype receptor 5 knockout. Ann. Surg. 235, 767-774.

Oda Y, Tanaka Y, Naruse T, Sasanabe R, Tsubamoto M, Funahashi H 2002 Expression of somatostatin receptor and effects of somatostatin analog on pancreatic endocrine tumors. Surg Today 32:690-694

Ohneda, A., Watanabe, K., Horigome, K., Sakai, T., Kai, Y., Oikawa, S., 1978. Abnormal response of pancreatic glucagon to glycemic changes in diabetes mellitus. J. Clin. Endocrinol. Metab 46, 504-510.

Orci, L., Baetens, D., Rufener, C., Amherdt, M., Ravazzola, M., Studer, P., Malaisse-Lagae, F., Unger, R. H., 1976. Hypertrophy and hyperplasia of somatostatin-containing D-cells in diabetes. Proc. Natl. Acad. Sci. U. S. A 73, 1338-1342.

Ostenson, C. G., Efendic, S., Grill, V., 1990. Abnormal regulation by glucose of somatostatin secretion in the perfused pancreas of NIDDM rats. Pancreas 5, 347-353.

Papachristou, D. N., Pham, K., Zingg, H. H., Patel, Y. C., 1989. Tissue-specific alterations in somatostatin mRNA accumulation in streptozocin-induced diabetes. Diabetes 38, 752-757.

Papotti, M., Bongiovanni, M., Volante, M., Allia, E., Landolfi, S., Helboe, L., Schindler, M., Cole, S. L., Bussolati, G., 2002. Expression of somatostatin receptor types 1-5 in 81 cases of gastrointestinal and pancreatic endocrine tumors. A correlative immunohistochemical and reverse-transcriptase polymerase chain reaction analysis. Virchows Arch. 440, 461-475.

Patel, R. C., Kumar, U., Lamb, D. C., Eid, J. S., Rocheville, M., Grant, M., Rani, A., Hazlett, T., Patel, S. C., Gratton, E., Patel, Y. C., 2002. Ligand binding to somatostatin receptors induces receptor-specific oligomer formation in live cells. Proc. Natl. Acad. Sci. U. S. A 99, 3294-3299.

Patel, Y. C., 1997. Molecular pharmacology of somatostatin receptor subtypes. J. Endocrinol. Invest 20, 348-367.

Patel, Y. C., 1999. Somatostatin and its receptor family. Front Neuroendocrinol. 20, 157-198.

Patel, Y. C., Greenwood, M. T., Panetta, R., Demchyshyn, L., Niznik, H., Srikant, C. B., 1995. The somatostatin receptor family. Life Sci. 57, 1249-1265.

Patel, Y. C., O'Neil, W., 1988. Peptides derived from cleavage of prosomatostatin at carboxyl- and amino-terminal segments. Characterization of tissue and secreted forms in the rat. J. Biol. Chem. 263, 745-751.

Patel, Y. C., Srikant, C. B., 1994. Subtype selectivity of peptide analogs for all five cloned human somatostatin receptors (hsstr 1-5). Endocrinology 135, 2814-2817.

Patel, Y. C., Wheatley, T., Ning, C., 1981. Multiple forms of immunoreactive somatostatin: comparison of distribution in neural and nonneural tissues and portal plasma of the rat. Endocrinology 109, 1943-1949.

Patton, G. S., Ipp, E., Dobbs, R. E., Orci, L., Vale, W., Unger, R. H., 1977. Pancreatic immunoreactive somatostatin release. Proc. Natl. Acad. Sci. U. S. A 74, 2140-2143.

Petersen, K. F., Sullivan, J. T., 2001. Effects of a novel glucagon receptor antagonist (Bay 27-9955) on glucagon-stimulated glucose production in humans. Diabetologia 44, 2018-2024.

Philippe, J., 1993. Somatostatin inhibits insulin-gene expression through a posttranscriptional mechanism in a hamster islet cell line. Diabetes 42, 244-249.

Portela-Gomes, G. M., Stridsberg, M., Grimelius, L., Oberg, K., Janson, E. T., 2000. Expression of the five different somatostatin receptor subtypes in endocrine cells of the pancreas. Appl. Immunohistochem. Mol. Morphol. 8, 126-132.

Pradayrol, L., Jornvall, H., Mutt, V., Ribet, A., 1980. N-terminally extended somatostatin: the primary structure of somatostatin-28. FEBS Lett. 109, 55-58.

Rahier, J., Goebbels, R. M., Henquin, J. C., 1983. Cellular composition of the human diabetic pancreas. Diabetologia 24, 366-371.

Rastogi, K. S., Lickley, L., Jokay, M., Efendic, S., Vranic, M., 1990. Paradoxical reduction in pancreatic glucagon with normalization of somatostatin and decrease in insulin in normoglycemic alloxan-diabetic dogs: a putative mechanism of glucagon irresponsiveness to hypoglycemia. Endocrinology 126, 1096-1104.

Raulf, F., Perez, J., Hoyer, D., Bruns, C., 1994. Differential expression of five somatostatin receptor subtypes, SSTR1-5, in the CNS and peripheral tissue. Digestion 55 Suppl 3, 46-53.

Raz, I., Rubinger, D., Popovtzer, M., Gronbaek, H., Weiss, O., Flyvbjerg, A., 1998. Octreotide prevents the early increase in renal insulin-like growth factor binding protein 1 in streptozotocin diabetic rats. Diabetes 47, 924-930.

Reaven, G. M., Chen, Y. D., Golay, A., Swislocki, A. L., Jaspan, J. B., 1987. Documentation of hyperglucagonemia throughout the day in nonobese and obese patients with noninsulin-dependent diabetes mellitus. J. Clin. Endocrinol. Metab 64, 106-110.

Reubi, J. C., Kappeler, A., Waser, B., Schonbrunn, A., Laissue, J., 1998. Immunohistochemical localization of somatostatin receptor sst2A in human pancreatic islets. J. Clin. Endocrinol. Metab 83, 3746-3749.

Rocheville, M., Lange, D. C., Kumar, U., Sasi, R., Patel, R. C., Patel, Y. C., 2000. Subtypes of the somatostatin receptor assemble as functional homo- and heterodimers. J. Biol. Chem. 275, 7862-7869.

Rohrer, S. P., Birzin, E. T., Mosley, R. T., Berk, S. C., Hutchins, S. M., Shen, D. M., Xiong, Y., Hayes, E. C., Parmar, R. M., Foor, F., Mitra, S. W., Degrado, S. J., Shu, M., Klopp, J. M., Cai, S. J., Blake, A., Chan, W. W., Pasternak, A., Yang, L., Patchett, A. A., Smith, R. G., Chapman, K. T., Schaeffer, J. M., 1998. Rapid identification of subtype-selective agonists of the somatostatin receptor through combinatorial chemistry. Science 282, 737-740.

Rohrer, S. P., Schaeffer, J. M., 2000. Identification and characterization of subtype selective somatostatin receptor agonists. J. Physiol Paris 94, 211-215.

Rossowski, W. J., Cheng, B. L., Jiang, N. Y., Coy, D. H., 1998. Examination of somatostatin involvement in the inhibitory action of GIP, GLP-1, amylin and adrenomedullin on gastric acid release using a new SRIF antagonist analogue. Br. J. Pharmacol. 125, 1081-1087.

Rossowski, W. J., Coy, D. H., 1993. Potent inhibitory effects of a type four receptor-selective somatostatin analog on rat insulin release. Biochem. Biophys. Res. Commun. 197, 366-371.

Rossowski, W. J., Coy, D. H., 1994. Specific inhibition of rat pancreatic insulin or glucagon release by receptor-selective somatostatin analogs. Biochem. Biophys. Res. Commun. 205, 341-346.

Rossowski, W. J., Gu, Z. F., Akarca, U. S., Jensen, R. T., Coy, D. H., 1994. Characterization of somatostatin receptor subtypes controlling rat gastric acid and pancreatic amylase release. Peptides 15, 1421-1424.

Samols, E., Bonner-Weir, S., Weir, G. C., 1986. Intra-islet insulin-glucagon-somatostatin relationships. Clin. Endocrinol. Metab 15, 33-58.

Samols, E., Stagner, J. I., 1990. Islet somatostatin--microvascular, paracrine, and pulsatile regulation. Metabolism 39, 55-60.

Samols, E., Stagner, J. I., Ewart, R. B., Marks, V., 1988. The order of islet microvascular cellular perfusion is B---A----D in the perfused rat pancreas. J. Clin. Invest 82, 350-353.

Saveanu, A., Gunz, G., Dufour, H., Caron, P., Fina, F., Ouafik, L., Culler, M. D., Moreau, J. P., Enjalbert, A., Jaquet, P., 2001. Bim-23244, a somatostatin receptor subtype 2- and 5-selective analog with enhanced efficacy in suppressing growth hormone (GH) from octreotide-resistant human GH-secreting adenomas. J. Clin. Endocrinol. Metab 86, 140-145.

Schauder, P., McIntosh, C., Arends, J., Frerichs, H., 1979. Effect of fasting on the release of insulin and somatostatin from perifused islets of Langerhans. Diabetes 28, 204-207.

Schindler, M., Holloway, S., Humphrey, P. P., Waldvogel, H., Faull, R. L., Berger, W., Emson, P. C., 1998. Localization of the somatostatin sst2(a) receptor in human cerebral cortex, hippocampus and cerebellum. Neuroreport 9, 521-525.

Schindler, M., Sellers, L. A., Humphrey, P. P., Emson, P. C., 1997. Immunohistochemical localization of the somatostatin SST2(A) receptor in the rat brain and spinal cord. Neuroscience 76, 225-240.

Schulz, S., Schreff, M., Schmidt, H., Handel, M., Przewlocki, R., Hollt, V., 1998. Immunocytochemical localization of somatostatin receptor sst2A in the rat spinal cord and dorsal root ganglia. Eur. J. Neurosci. 10, 3700-3708.

Segers, O., De Vroede, M., Michotte, Y., Somers, G., 1989. Basal and tolbutamide-induced plasma somatostatin in healthy subjects and in patients with diabetes and impaired glucose tolerance. Diabet. Med. 6, 232-238.

Seghers, V., Nakazaki, M., DeMayo, F., Aguilar-Bryan, L., Bryan, J., 2000. Sur1 knockout mice. A model for K(ATP) channel-independent regulation of insulin secretion. J. Biol. Chem. 275, 9270-9277.

Service, F. J., McMahon, M. M., O'Brien, P. C., Ballard, D. J., 1991. Functioning insulinoma--incidence, recurrence, and long-term survival of patients: a 60-year study. Mayo Clin. Proc. 66, 711-719.

Shah, P., Basu, A., Basu, R., Rizza, R., 1999. Impact of lack of suppression of glucagon on glucose tolerance in humans. Am. J. Physiol 277, E283-E290.

Shah, P., Vella, A., Basu, A., Basu, R., Schwenk, W. F., Rizza, R. A., 2000. Lack of suppression of glucagon contributes to postprandial hyperglycemia in subjects with type 2 diabetes mellitus. J. Clin. Endocrinol. Metab 85, 4053-4059.

Shimon, I., Taylor, J. E., Dong, J. Z., Bitonte, R. A., Kim, S., Morgan, B., Coy, D. H., Culler, M. D., Melmed, S., 1997a. Somatostatin receptor subtype specificity in human fetal pituitary cultures. Differential role of SSTR2 and SSTR5 for growth hormone, thyroid-stimulating hormone, and prolactin regulation. J. Clin. Invest 99, 789-798.

Shimon, I., Yan, X., Taylor, J. E., Weiss, M. H., Culler, M. D., Melmed, S., 1997b. Somatostatin receptor (SSTR) subtype-selective analogues differentially suppress in vitro growth hormone and prolactin in human pituitary adenomas. Novel potential therapy for functional pituitary tumors. J. Clin. Invest 100, 2386-2392.

Siehler, S., Seuwen, K., Hoyer, D., 1999. Characterisation of human recombinant somatostatin receptors. 1. Radioligand binding studies. Naunyn Schmiedebergs Arch. Pharmacol. 360, 488-499.

Singh, V., Brendel, M. D., Zacharias, S., Mergler, S., Jahr, H., Wiedenmann, B., Bretzel, R. G., Plockinger, U., Strowski, M. Z., 2007a. Characterization of Somatostatin Receptor Subtype-Specific Regulation of Insulin and Glucagon Secretion: An in Vitro Study on Isolated Human Pancreatic Islets. J. Clin. Endocrinol. Metab 92, 673-680.

Singh, V., Grotzinger, C., Nowak, K. W., Zacharias, S., Goncz, E., Pless, G., Sauer, I. M., Eichhorn, I., Pfeiffer-Guglielmi, B., Hamprecht, B., Wiedenmann, B., Plockinger, U., Strowski, M. Z., 2007b. Somatostatin receptor subtype-2-deficient mice with diet-induced obesity have hyperglycemia, nonfasting hyperglucagonemia, and decreased hepatic glycogen deposition. Endocrinology 148, 3887-3899.

Skare, S., Dahl-Jorgensen, K., Hanssen, K. F., Norman, N., 1985. Increased peripheral venous somatostatin concentration and decreased glucagon response to arginine in patients with insulin dependent diabetes mellitus without residual B-cell function. Increased plasma SRIF in IDDM. Acta Endocrinol. (Copenh) 109, 517-521.

Stefan, Y., Grasso, S., Perrelet, A., Orci, L., 1983. A quantitative immunofluorescent study of the endocrine cell populations in the developing human pancreas. Diabetes 32, 293-301.

Strowski, M. Z., Cashen, D. E., Birzin, E. T., Yang, L., Singh, V., Jacks, T. M., Nowak, K., Rohrer, S. P., Patchett, A. A., Smith, R. G., Schaeffer, J. M., 2006. Antidiabetic activity of a highly potent and selective non-peptide somatostatin receptor subtype-2 agonist. Endocrinology 147, 4664-4673.

Strowski, M. Z., Kohler, M., Chen, H. Y., Trumbauer, M. E., Li, Z., Szalkowski, D., Gopal-Truter, S., Fisher, J. K., Schaeffer, J. M., Blake, A. D., Zhang, B. B., Wilkinson, H. A., 2003. Somatostatin receptor subtype 5 regulates insulin secretion and glucose homeostasis. Mol. Endocrinol. 17, 93-106.

Strowski, M. Z., Parmar, R. M., Blake, A. D., Schaeffer, J. M., 2000. Somatostatin inhibits insulin and glucagon secretion via two receptors subtypes: an in vitro study of pancreatic islets from somatostatin receptor 2 knockout mice. Endocrinology 141, 111-117.

Taborsky, G. J., Jr., 1983. Evidence of a paracrine role for pancreatic somatostatin in vivo. Am. J. Physiol 245, E598-E603.

Taborsky, G. J., Jr., Ensinck, J. W., 1984. Contribution of the pancreas to circulating somatostatin-like immunoreactivity in the normal dog. J. Clin. Invest 73, 216-223.

Takano, A., Haruta, T., Iwata, M., Usui, I., Uno, T., Kawahara, J., Ueno, E., Sasaoka, T., Kobayashi, M., 2001. Growth hormone induces cellular insulin resistance by uncoupling phosphatidylinositol 3-kinase and its downstream signals in 3T3-L1 adipocytes. Diabetes 50, 1891-1900.

Taniyama, Y., Suzuki, T., Mikami, Y., Moriya, T., Satomi, S., Sasano, H., 2005. Systemic distribution of somatostatin receptor subtypes in human: an immunohistochemical study. Endocr. J. 52, 605-611.

Tirone, T. A., Norman, M. A., Moldovan, S., Demayo, F. J., Wang, X. P., Brunicardi, F. C., 2003. Pancreatic somatostatin inhibits insulin secretion via SSTR-5 in the isolated perfused mouse pancreas model. Pancreas 26, e67-e73.

Tulipano, G., Soldi, D., Bagnasco, M., Culler, M. D., Taylor, J. E., Cocchi, D., Giustina, A., 2002. Characterization of new selective somatostatin receptor subtype-2 (sst2) antagonists, BIM-23627 and BIM-23454. Effects of BIM-23627 on GH release in anesthetized male rats after short-term high-dose dexamethasone treatment. Endocrinology 143, 1218-1224.

Unger, R. H., 1975. Letter: Glucagon in pathogenesis of diabetes. Lancet 1, 1036-2.

Unger, R. H., 1976. The Banting Memorial Lecture 1975. Diabetes and the alpha cell. Diabetes 25, 136-151.

Unger, R. H., Orci, L., 1975. The essential role of glucagon in the pathogenesis of diabetes mellitus. Lancet 1, 14-16.

Unger, R. H., Orci, L., 1977. Possible roles of the pancreatic D-cell in the normal and diabetic states. Diabetes 26, 241-244.

Usenmez, T., Yildiz, O., Oktenli, C., Ozgurtas, T., Kutlu, M., 2000. Octreotide administration in diabetic rats: effects on renal function and morphology. J. Diabetes Complications 14, 53-59.

van der Hoek J., de Herder, W. W., Feelders, R. A., van der Lely, A. J., Uitterlinden, P., Boerlin, V., Bruns, C., Poon, K. W., Lewis, I., Weckbecker, G., Krahnke, T., Hofland, L. J., Lamberts, S. W., 2004. A single-dose comparison of the acute effects between the new somatostatin analog SOM230 and octreotide in acromegalic patients. J. Clin. Endocrinol. Metab 89, 638-645.

Wang, X. P., Norman, M., Yang, J., Liu, S. H., Magnusson, J., Demayo, F. J., Brunicardi, F. C., 2005. The effect of global SSTR5 gene ablation on the endocrine pancreas and glucose regulation in aging mice. J. Surg. Res. 129, 64-72.

Wang, X. P., Norman, M., Yang, J., Magnusson, J., Kreienkamp, H. J., Richter, D., Demayo, F. J., Brunicardi, F. C., 2006. Alterations in glucose homeostasis in SSTR1 gene-ablated mice. Mol. Cell Endocrinol. 247, 82-90.

Wang, X. P., Norman, M. A., Yang, J., Cheung, A., Moldovan, S., Demayo, F. J., Brunicardi, F. C., 2004. Double-gene ablation of SSTR1 and SSTR5 results in hyperinsulinemia and improved glucose tolerance in mice. Surgery 136, 585-592.

Weckbecker, G., Briner, U., Lewis, I., Bruns, C., 2002. SOM230: a new somatostatin peptidomimetic with potent inhibitory effects on the growth hormone/insulin-like growth factor-I axis in rats, primates, and dogs. Endocrinology 143, 4123-4130.

Yang, L., Berk, S. C., Rohrer, S. P., Mosley, R. T., Guo, L., Underwood, D. J., Arison, B. H., Birzin, E. T., Hayes, E. C., Mitra, S. W., Parmar, R. M., Cheng, K., Wu, T. J., Butler, B. S., Foor, F., Pasternak, A., Pan,

Y., Silva, M., Freidinger, R. M., Smith, R. G., Chapman, K., Schaeffer, J. M., Patchett, A. A., 1998. Synthesis and biological activities of potent peptidomimetics selective for somatostatin receptor subtype 2. Proc. Natl. Acad. Sci. U. S. A 95, 10836-10841.

Zatelli, M. C., Tagliati, F., Piccin, D., Taylor, J. E., Culler, M. D., Bondanelli, M., Degli Uberti, E. C., 2002. Somatostatin receptor subtype 1-selective activation reduces cell growth and calcitonin secretion in a human medullary thyroid carcinoma cell line. Biochem. Biophys. Res. Commun. 297, 828-834.

Zatelli, M. C., Tagliati, F., Taylor, J. E., Rossi, R., Culler, M. D., Degli Uberti, E. C., 2001. Somatostatin receptor subtypes 2 and 5 differentially affect proliferation in vitro of the human medullary thyroid carcinoma cell line tt. J. Clin. Endocrinol. Metab 86, 2161-2169.

Zheng, H., Bailey, A., Jiang, M. H., Honda, K., Chen, H. Y., Trumbauer, M. E., Van der Ploeg, L. H., Schaeffer, J. M., Leng, G., Smith, R. G., 1997. Somatostatin receptor subtype 2 knockout mice are refractory to growth hormone-negative feedback on arcuate neurons. Mol. Endocrinol. 11, 1709-1717.

Table 1. Expression of SSTRs in rodent endocrine pancreatic A-, B-, C-, and D-cells detected by immunohistochemistry.

	SSTR1	SSTR2	SSTR3	SSTR4	SSTR5
A-cell					
Kimura et al	n.d.	+	n.d.	n.d.	n.d.
Hunyady et al.	n.d.	++	n.d.	n.d.	n.d.
Mitra et al	n.d.	n.d.	n.d.	n.d.	-
Ludvigsen et al. (rat)	≈40	≈80	≈25	<20	≈90
Ludvigsen et al. (mouse)	≈20	<70	<20	>20	<70
B-cell					
Kimura et al	n.d.	++	n.d.	n.d.	n.d.
Hunyady et al.	n.d.	(+)	n.d.	n.d.	n.d.
Mitra et al	n.d.	n.d.	n.d.	n.d.	+
Ludvigsen et al. (rat)	≈45	≈40	≈43	<40	>55
Ludvigsen et al. (mouse)	>95	≈90	≈65	≈40	≈90
D-cell					
Kimura et al	n.d.	++	n.d.	n.d.	n.d.
Hunyady et al.	n.d.	-	n.d.	n.d.	n.d.
Mitra et al	n.d.	n.d.	n.d.	n.d.	-
Ludvigsen et al. (rat)	≈60	>70	>70	≈80	<40
Ludvigsen et al. (mouse)	≈40	≈50	≈50	>60	<40
PP-cell					
Kimura et al	n.d.	+	n.d.	n.d.	n.d.
Hunyady et al.	n.d.	++	n.d.	n.d.	n.d.
Mitra et al	n.d.	n.d.	n.d.	n.d.	-
Ludvigsen et al. (rat)	≈30	≈10	<10	≈10	≈20
Ludvigsen et al. (mouse)	>40	>60	≈20	>70	≈70

Numbers represent % of SSTR-immunopositive cells. n.d.: not done. -: negative, (+): weak positive, +: positive, ++: strong positive.

Table 2. Immunochemical detection of changes of SSTR expression in pancreatic A-, B-, D- and PP-cells of female NOD mice (animal model of autoimmune type 1 diabetes) in comparison to non-diabetic ICR control mice (Ludvigsen et al., 2005).

Cell type	SSTR1	SSTR2	SSTR3	SSTR4	SSTR5
A	↑	→	↑	↑	↑
B	↓	none	→	none	↓
D	↓	(↑)	↓	→	→
PP	→	↑	none	→	↑

↓: downregulated; ↑: upregulated; →: unchanged SSTR expression; none: complete loss of SSTR expression in NOD mice as compared to non-diabetic ICR control mice.

Table 3. Quantitative and qualitative expression of SSTRs in human pancreatic A-, B, D-and PP-cells using antibodies. Numbers represent % of SSTR-immunopositive cells.

	SSTR1	SSTR2	SSTR3	SSTR4	SSTR5
A-cell					
Kumar et al.	26	89	14	0	35
Portela-Gomes et al.	71	91	93	80	6
Papotti et al.	n.d.	70	70	n.d.	80
Reubi et al	n.d.	+	n.d.	n.d.	n.d.
Kimura et al.	n.d.	+	n.d.	n.d.	n.d.
Taniyama et al.	n.d.	+	+	n.d.	(+)
B-cell					
Kumar et al.	100	46	28	17	87
Portela-Gomes	100	85	97	81	96
Papotti et al.	n.d.	75	60	n.d.	90
Reubi et al	n.d.	+	n.d.	n.d.	n.d.
Kimura et al.	n.d.	++	n.d.	n.d.	n.d.
Taniyama et al.	n.d.	+	(+)	n.d.	++
D-cell					
Kumar et al.	12	11	14	0	75
Portela-Gomes	70	66	87	100	99
Papotti et al.	n.d.	55	33	n.d.	95
Kimura et al.	n.d.	++	n.d.	n.d.	n.d.
Taniyama et al.	n.d.	-	-	n.d.	(+)
PP-cell					
Portela-Gomes	83	17	90	86	0
Kimura et al.	n.d.	+	n.d.	n.d.	n.d.

n.d.: not done. -: negative, (+): weak positive, +: positive, ++: strong positive.

Table 4. Detection of SSTR expression in neuroendocrine tumors by RT-PCR and immunohistochemistry.

	SSTR1	SSTR2	SSTR3	SSTR4	SSTR5
Insulinoma					
Kubota et al. [§], n=4	4/4	3/4	2/4	4/4	0/4
de Sa et al., 2006 [§], n=18	100%	89%	100%	22%	100%
Bertherat et al. [§], n=27	50%	70%	15%	20%	70%
Papotti et al. [§,#], n=19-25	89% [§]	60%[#]	60%[#]	40%[§]	50%[#]
Kulaksiz et al. [§], n=36	31%	58%	78%	n.d.	78%
Wulbrand et al. [§], n=10	7/10	9/10	1/10	2/10	6/10
Glucagonoma					
Kubota et al. [§], n=2	2/2	2/2	2/2	2/2	0/2
Papotti et al. [§,#], n=1-5	1/1[§]	5/5[#]	2/5[#]	0/1[§]	3/5[#]
Gastrinoma					
Papotti et al. [§,#], n=3-8	2/4[§]	8/8[#]	5/8[#]	1/3[§]	7/8[#]
Kulaksiz et al. [§], n=33	30%	100%	79%	n.d	76%
Wulbrand et al. [§], n=10	9/9	9/9	2/9	2/9	9/9
Somatostatinoma					
Papotti et al. [§,#], n=3	n.d.	2/3[#]	2/3[#]	n.d.	3/3[#]

§: RT-PCR, #: Immunohistochemistry, n: number of tumors analyzed. , n.d.: not done,