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Table 1: expression of sst sybtypes in cells and tissues of the human immune system

Tissue	sst ₁	sst ₂	sst ₃	sst ₄	sst ₅	After reference(s)
Bone marrow		+				(Oomen et al., 2000)
Thymus	+	+	+			(Ferone et al., 2002, Ferone et al., 1999)
Spleen		+				(Reubi et al., 2001)
PBMC		+	+			(Lichtenauer-Kaligis et al., 2004)
T-lymphocytes			+			(Lichtenauer-Kaligis et al., 2004)
B-lymphocytes			+			(Lichtenauer-Kaligis et al., 2004)
Monocytes/ macrophages/ dendritic cells		+				(Dalm et al., 2003c, Lichtenauer-Kaligis et al., 2004)
T- and B-cell lines		+	+			(van Hagen et al., 1999)

Future clinical prospects in somatostatin/cortistatin/somatostatin receptor field

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Abstract

Somatostatin receptors (sst), somatostatin (SS) and cortistatin (CST) are widely expressed in the various systems in the human and rodent organisms and are “responsible” for maintaining homeostasis, which is essential for survival. Because of their broad expression pattern sst, SS and CST interactions may play regulatory roles in both physiology and pathophysiology in mammalian organisms. SS analogue treatment strategies as well as the use of SS analogues for diagnostic purposes have been established in diseases of different origins. This review focuses on the currently determined role for SS analogues in today’s clinical practice and the potential clinical prospects for SS, CST and sst interactions in the future, with a focus on neuroendocrine – and non-neuroendocrine tumours and immune-mediated diseases. Moreover, the role of new SS analogues and new insights in sst physiology will be discussed.

Introduction

In mammals, proteolytic processing of a 116-amino acid prepro-SS results in the formation of 2 biologically active forms of SS, consisting of 14 and 28 amino acids, respectively (Patel and Galanopoulou, 1995). The amino acid residues Phe⁷, Trp⁸, Lys⁹ and Thr¹⁰ are essential for binding of both SS isoforms to their 5 known receptors, sst₁₋₅ (Veber et al., 1979), which are G-protein coupled seven transmembrane receptors, having an N-terminal extracellular domain and C-terminal intracellular domain (Patel, 1999). Via binding to its receptors SS exerts its multiple effects, which are described extensively in the papers of the present journal. SS is widely expressed throughout the human body, like for instance in the central nervous system, gastro-intestinal tract and endocrine glands (Boehm and Betz, 1997; Chesselet et al., 1995; Lamberts, 1988; Reichlin, 1983b; Reichlin, 1983a). In these tissues/systems SS exerts a mainly inhibitory role on secretion processes (Brazeau, 1986; Lamberts et al., 1996; Reichlin, 1983a). In addition, SS was also shown to have antiproliferative effects on different cell types in vitro.

Recently, the group of de Lecea and co-workers isolated a DNA clone encoding a novel neuropeptide from rat brain, called CST (de Lecea et al., 1996). Comparable to SS-14 and SS-28, proteolytic processing of procortistatin in rat results in the production of two isoforms, CST-14 and CST-29. The human peptide consists of 17 amino acids (de Lecea et al., 1997; Fukusumi et al., 1997). Because of its high structural resemblance to SS, CST binds with high affinity to the 5 known sst (Fukusumi et al., 1997). Recent studies have addressed the question whether CST is also more widely expressed than previously assumed, i.e. in the central nervous system. Wide expression of CST mRNA was detected in tissues throughout the human body (Dalm et al., 2004b). Moreover, a novel putative receptor has been described recently. This receptor, named MrgX2, has been shown to bind CST with highest affinity of over 2500 peptides evaluated, whereas SS only binds with low affinity to this receptor (Robas et al., 2003). These findings suggest that CST may act via either the sst or the MrgX2, which in term may explain some differences in effects between SS and CST. Our current knowledge on expression patterns of sst, SS and CST has opened a new area of research, in which the potential functional significance of these neuropeptides, apart from their known role in the brain, in different tissues throughout the human body is investigated.

The present review aims to give a brief overview of the potential (future) functional prospects of SS, CST and sst interactions in the various organ systems and discusses potential strategies for further research. We will focus on the potential clinical significance of SS and CST and their analogues in the fields of central nervous system abnormalities, endocrine actions, their place in oncology and immunology. Furthermore, the diagnostic and therapeutic significance of the development of new SS/CST analogues will be discussed.

Central actions in the SS/CST and sst network

Sleep regulation

de Lecea et al. identified for the first time the DNA clone encoding CST in rat cortex (de Lecea et al., 1996). Most of the actions of CST have been designated to the regulation of behaviour, sleep and memory mechanisms localized in the brain region. Compared to SS, CST shows both overlapping and differential effects on these various mechanisms. Both compounds seem to depress neuronal activity in the hippocampus (de Lecea et al., 1996),

reduce development of seizures (Braun et al., 1998) and can deteriorate memory consolidation (Sanchez-Alavez et al., 2000). On the other hand, many differences in effects between SS and CST have been described. For example, CST-treated rats showed clear hypoactive behaviour and the electroencephalogram (EEG) showed a dramatic increase in cortical slow waves (de Lecea et al., 1996). Subsequently, after administration of CST, rats spent more time in slow-wave sleep and less time in Rapid Eye Movement (REM) sleep. On the other hand, the administration of SS results in sleep periods dominated by REM sleep, without significantly affecting the other phases of sleep (de Lecea et al., 1996; Feige et al., 1987; Fukusumi et al., 1997). Moreover, it has been demonstrated that CST expression is upregulated during sleep deprivation in rats. During sleep deprivation also upregulation of SS has been demonstrated in the brain (Toppila et al., 1997; Toppila et al., 1996). This suggests that SS and CST both have sleep regulatory functions and probably interplay in the regulation of sleep, both in their own specific way. Previous studies demonstrated that acetylcholine (ACh) is present at low concentration in the cortex during slow-wave sleep, and higher concentrations of ACh are associated with wakefulness and REM sleep (Shiromani et al., 1987). Therefore, the question was addressed whether CST produces its sleep promoting effects by modulating ACh activity. It has been shown that CST antagonizes the effects of ACh (de Lecea et al., 1996), while SS is known to enhance the effects of ACh (Mancillas et al., 1986). Because of the distinct actions of SS and CST it was hypothesized that, instead of both peptides acting on the same sst, a specific receptor for CST might be responsible for the differences in the above mentioned effects (Calbet et al., 1999; Criado et al., 1999). With the detection of the more CST-specific receptor MrgX2 (Robas et al., 2003) and its expression in the brain region, an explanation for distinct actions between both peptides may be found. However, binding affinity of CST for the MrgX2 receptor is relatively low (Robas et al., 2003).

Summarizing, in behaviour en sleep regulation both SS and CST seems to play important regulatory roles, whereas the clinical significance of both peptides regulating these processes needs to be evaluated more extensively.

Epilepsy

Epilepsy is characterized by abnormal hyperexcitation, which can include several different brain regions. Temporal lobe epilepsy (TLE) involves the hippocampus (Sloviter, 1994). In tissues removed from patients with TLE a selective loss of SS containing neurons was found in the hilus of the dentate gyrus (de Lanerolle et al., 1989; Mathern et al., 1995). Comparable results were found in animal models for epilepsy (Mitchell et al., 1995; Sloviter, 1987) in

which SS containing neuronal loss can extend beyond the hilus to the rest of the hippocampus (Lahtinen et al., 1993). Recent studies have investigated the pathways involved in SS neuron loss in epilepsy, and it seems that the extracellular signal-regulated kinase/mitogen-activated protein kinase (ERK/MAPK) pathway may be involved (Choi et al., 2007). The function of these SS neurons and the consequences of their loss are unknown. However, the majority of SS interneurons make inhibitory synapses onto primary hippocampal neurons (Freund and Buzsaki, 1996; Leranth et al., 1990), suggesting their involvement in inhibitory processes. The loss of SS neurons in early stages of epilepsy may contribute to subsequent abnormal hippocampal hyperexcitability (Freund and Buzsaki, 1996; Leranth et al., 1990).

Intracerebroventricular and intrahippocampal injections of SS and SS analogues have been shown to modulate seizure activity in animal models. Early studies suggested that SS had a stimulatory effect on seizures (Higuchi et al., 1983; Perlin et al., 1987), however, more recent studies, in which SS was directly injected into the hippocampus, have demonstrated inhibitory effects on electrical seizures recorded in vivo (Vezzani et al., 2000; Vezzani et al., 1991).

Moreover, administration of SS to hippocampal CA1 and CA3 pyramidal neurons reduces epileptiform events in hippocampal slices (Tallent and Siggins, 1999) and SS knock-out mice show an increase in severity of seizures induced by kainate, a glutamate receptor analogue (Buckmaster et al., 2002). In rat brain ss_{22} selective agonists have been shown to decrease seizure severity (Vezzani and Hoyer, 1999). These findings in animal models both in vitro and in vivo show an important role for SS in regulating seizure activities. The exact mechanisms remain to be determined in future studies in transgenic and knock-out mice which allows for temporally and regionally controlled expression and deletion (Baraban and Tallent, 2004). The potential clinical significance of SS or its analogues with respect to therapeutical options in epilepsy therefore seems to be still far ahead.

Neuroendocrine disorders

SS was initially identified as an growth hormone release inhibiting factor (Brazeau et al., 1973) from the ovine hypothalamus. SS in animals and human, however, was found to exert broader inhibitory effects on hormone secretion, like insulin and glucagon. These inhibitory effects have formed the basis for the application of SS analogues in treatment of endocrine tumours. In the present chapter, a brief overview will be presented on the current knowledge and work-in-progress on SS analogue based therapy and the visualization of endocrine tumours.

Acromegaly

Acromegaly is a disorder, characterized by hypersecretion of growth hormone (GH), mainly by pituitary adenomas, leading to elevated circulating GH and insulin-like growth factor I (IGF-I) levels. Over the years treatment strategies consisted of surgery, irradiation and medical treatment in order to induce tumour shrinkage and normalization of GH and IGF-I levels (Melmed et al., 1998). Therapy aims for reduction of the risk of long-term complications, like development of malignant neoplasms, cardio- and cerebrovascular disease, respiratory and metabolic dysfunction (Rajasoorya et al., 1994). In GH-secreting pituitary adenomas ss_{t2} and ss_{t5} are the predominantly expressed sst (Hofland et al., 2004; Jaquet et al., 2000; Murabe et al., 1996; Reubi et al., 2001). The introduction of the long-acting SS analogues octreotide and lanreotide in treatment of acromegalic patients (Bauer et al., 1982; Lamberts et al., 1985), which were shown to decrease GH levels and clinical signs and symptoms, has turned these peptides into the worldwide first medical treatment options for acromegaly (Lamberts et al., 1996). Recent studies have addressed in more detail the involvement of the different sst subtypes in regulating responses to SS analogues. The expression of ss_{t2} was found to be positively correlated to the in vivo GH suppression induced by octreotide (Hofland et al., 2004; Saveanu et al., 2001a; Taboada et al., 2007). In primary cultures of GH secreting pituitary adenomas, new ss_{t2} selective SS analogues, with higher affinity to ss_{t2} compared to octreotide and lanreotide, show a more potent effect on inhibition of GH secretion. However, in other cultures ss_{t5} selective SS analogues were found to be more potent (Shimon et al., 1997). Moreover, the combined activation of ss_{t2} and ss_{t5} results in additive inhibitory effects on GH secretion (Shimon et al., 1997). In a study by Ren and co-workers (Ren et al., 2003) it was demonstrated that a ss_{t2} selective antagonist was able to reverse the GH suppressive effects of ss_{t2}/ss_{t5} biselective agonists or that of ss_{t2} and ss_{t5} agonists in combination, which suggests a functional interaction between both sst subtypes. The additive GH-suppressive effect of activating both ss_{t2} and ss_{t5} led to the development of new SS analogues with binding affinities to different sst subtypes. As an example, the bi-selective compound BIM-23244, which binds with high affinity to both ss_{t2} and ss_{t5} , was found to more potently inhibit GH secretion in a series of partially octreotide-resistance adenomas (Saveanu et al., 2001a). These adenomas expressed lower levels of ss_{t2} and higher levels of ss_{t5} , when compared to the octreotide-sensitive adenomas (Saveanu et al., 2001a). This suggests, that in adenomas with a low expression of ss_{t2} , ss_{t5} may be of more importance

in regulating GH secretion. A second novel SS analogue, SOM230, with a broad sst binding profile (with a 25-, 5- and 40 times higher binding affinity to sst₁, sst₃, and sst₅ receptors respectively, and 2.5 times lower affinity to sst₂, when compared to octreotide (Bruns et al., 2002)) was found to have more potent inhibitory effects compared to octreotide on GH secretion in GH-secreting pituitary adenomas in vitro (Hofland et al., 2004) and in primary cultures from human fetal pituitary cells (Murray et al., 2004). This more potent effect may be due to the combined activation of both sst₂ and sst₅ by SOM230. In a clinical trial in 12 patients with active acromegaly a single injection of octreotide was compared to SOM230 (van der Hoek et al., 2004). Comparable effects on GH secretion were found in 8 patients, while in 3 patients a significantly enhanced suppression was observed. The observation that SOM230 potently inhibits the secretion of GH in tumours expressing low levels of sst₂ and high levels of sst₅ indeed suggests an important role for sst₅ in regulating GH secretion in non-octreotide responders. The enhanced activity is explained by higher sst₅ levels and higher binding affinity to sst₅ of SOM230. Since SOM230 is able of regulating GH secretion in octreotide responders and partial responders, SOM230 has a clear advantage over octreotide, and more patients may be biochemically controlled in long-term medical treatment. Finally, also sst₁ may be involved in controlling GH secretion. Two sst₁ selective SS analogues, BIM23296 and BIM23745 significantly inhibited GH secretion from GH-secreting pituitary adenomas in vitro, while no effects of octreotide were observed (Matrone et al., 2004; Zatelli et al., 2003). In a recent study, using the recently discovered SS-like peptide CST, patients with active acromegaly were injected with CST and significant inhibition of GH was observed in these patients, comparable to the effects obtained by SS infusion (Grottoli et al., 2006). As both peptides exert comparable effects it was hypothesized that both SS and CST exert their effects via the same receptors, ie sst, in these tumours. It is therefore unlikely that CST plays a role in treatment of these disorders.

Cushing's Disease

Cushing's disease is characterized by hypersecretion of adrenocorticotropin hormone (ACTH) by the pituitary gland, resulting in overproduction of cortisol by hyperplastic adrenocortical glands (Newell-Price et al., 1998). In Cushing's disease transsphenoidal surgery is the treatment of choice, results reporting success rates between 50 and almost 90 % (Knappe and Ludecke, 1996; Mampalam et al., 1988; Swearingen et al., 1999). If surgery fails,

radiotherapy may be used (Sonino et al., 1996). However, none of the treatment strategies ensures full and permanent cure, as the rate of recurrence of disease varies between 5 and 24 % (Chee et al., 2001; Estrada et al., 2001; Rees et al., 2002; Yap et al., 2002). The expression of sst in ACTH-secreting pituitary adenomas has led to studies investigating the potential significance of SS analogues in treatment of Cushing's disease. Initial studies in small numbers of patients with the first clinically available SS analogue octreotide showed that octreotide had no significant effects in reducing ACTH levels (Ambrosi et al., 1990; Lamberts et al., 1989a; Stalla et al., 1994). Previous studies have demonstrated that glucocorticoids can downregulate sst receptor expression (Schonbrunn, 1982). In an hypercortisolemic state, as in Cushing's disease, sst receptors may be downregulated on pituitary tumour cells, which may explain why SS analogues lack an inhibitory effect on ACTH secretion in Cushing's disease (Lamberts et al., 1989b). However, recent progress in multiligand SS analogue development, i.e. SOM230, has again raised interest in potential benefits of these new compounds in Cushing's disease (Lewis et al., 2003). On the other hand, relatively little is known about quantitative sst receptor subtype expression in ACTH-secreting pituitary tumours. Highest frequency of expression of sst₂ (88%) and sst₅ (86%) and to a lesser extent sst₁ (63%) has been reported (Greenman and Melmed, 1994; Miller et al., 1995; Nielsen et al., 2001; Panetta and Patel, 1995). Sst₂ expression is apparently low, resulting in the lack of inhibitory effects of the sst₂-selective SS analogue octreotide. Recently, it has been demonstrated that sst₅ may have a regulatory role on ACTH secretion by human corticotroph adenoma cells (Hofland et al., 2005). In murine corticotroph adenoma cells it was demonstrated that SOM230 more potently inhibited ACTH secretion in basal and CRH-stimulated conditions (Hofland et al., 2005). Glucocorticoid treatment showed remarkable differences with respect to the role of sst₂ and sst₅ in controlling ACTH secretion (van der Hoek et al., 2005). The suppressive effects of octreotide were almost completely blocked, while the inhibitory effects of SOM230 remained.

RT-PCR studies indeed showed that *sst*₂ mRNA expression was downregulated upon dexamethason treatment, while *sst*₅ mRNA expression was more resistant to dexamethasone. In a small series of human corticotroph adenomas more potent effects of SOM230 on ACTH secretion were found (inhibition in 3 out of 5 cultures) compared to octreotide (inhibition in 1 culture) (Hofland et al., 2005). These findings were in line with relative high levels of *sst*₅ mRNA expression in these cells (Hofland et al., 2005), while expression of *sst*₂ was low, also explaining the lack of effects of *sst*₂ selective agonists in patients with Cushing's disease. These findings suggest a potential therapeutical role for the new SS analogue, SOM230, in Cushing's disease as the *sst*₅ is the subtype preferentially expressed and shows relative resistance to glucocorticoids and seems to be involved in decreasing ACTH levels. Future clinical studies will be performed to determine the place of new, multiligand or *sst*₅-selective SS analogues in treatment strategies for Cushing's disease.

TSH-secreting pituitary adenomas

TSH-secreting pituitary adenoma is a relatively rare disorder and surgery is the most important treatment approach, normalizing thyroid hormone levels in approximately 44% of patients (Beck-Peccoz et al., 1996a; Beck-Peccoz et al., 1996b). In patients treated with octreotide, 80% showed normalization of TSH levels, while significant tumour shrinkage was observed in 50% (Chanson et al., 1993; Comi et al., 1987). In a very recent study it was demonstrated that *sst*₂ is the *sst* subtype predominantly expressed in a series of TSH-secreting adenomas (Horiguchi et al., 2007), and the patient with highest expression of *sst*₂ showed marked shrinkage of the tumour on octreotide treatment. These data suggest that *sst*₂ is involved in control of TSH secretion and SS analogues form a treatment modality in these tumours.

Prolactinomas

Dopamin agonists have until now been shown to be highly active in medical treatment of prolactinomas (Colao et al., 2002; Webster, 1999). However, some patients seem to be resistant or partially responsive to dopamine agonist therapy. It is therefore questioned whether SS analogue therapy may contribute to medical treatment regimens in these patients. In an in vitro experiment it was demonstrated that SOM-230 potently inhibited prolactin secretion in prolactinoma samples (Hofland et al., 2004), and the percentage of inhibition correlated with the sst₅ mRNA expression levels, which is the predominant sst subtype expressed. On the other hand, octreotide inhibited prolactin secretion to a much lesser extent, which may be explained by the low expression of sst₂ in prolactinomas as demonstrated previously (Jaquet et al., 1999). It seems that sst₅ therefore is the major sst subtype influenced by SS analogue therapy. However, it should be mentioned that the group of Jaquet et al. demonstrated that the effects of sst₅ selective compounds on prolactinoma cells are superimposable, at higher concentrations to those of the dopamine agonists, but not additive, particularly in adenomas resistant to dopaminergic suppression of prolactin release (Jaquet et al., 1999). In a number of recent studies both in vivo and in vitro it was found that SS and CST exerted inhibitory effects on prolactin secretion by prolactinomas as well (Grottoli et al., 2006; Rubinfeld et al., 2006). In a series of three cultured prolactinomas, CST significantly inhibited prolactin secretion, similar to effects induced by the sst₅ selective agonist BIM23206, while the sst₂ selective agonist BIM23210 only exerted significant effects in one prolactinoma (Rubinfeld et al., 2006). In an in vivo study a significant, comparable reduction in prolactin levels was obtained after infusion with either SS or CST (Grottoli et al., 2006). These effects may be explained by their high binding affinities to both sst₂ and sst₅, mainly by acting via the predominantly expressed sst₅, while on the other hand sst₂ selective agonists were found to have limited effects on prolactin levels (Lamberts et al., 1986). The clinical importance of sst analogue therapy in prolactinomas remains uncertain as their effects seem not to be additive to the effects of the widely used dopamine agonist treatment regimens.

Clinically non-functioning pituitary adenomas

Clinically non-functioning pituitary adenomas (NFAs) form a heterogeneous group of tumours, some of them secreting intact follicle stimulating hormone/luteinizing hormone and/or their α and β subunits. Macroadenomas often come to medical attention due to mass effects, resulting in visual field defects or hypopituitarism. Various sst subtypes are expressed in NFAs, which led to the hypothesis that SS analogues may be involved in tumour control.

However, in limited clinical trials only a disappointing tumour control rate of around 11-13 % was reported (Colao et al., 2003). A recent study demonstrated, again in vitro, that sst₁, sst₂ and sst₅ selective agonists exert inhibitory effects on cell viability in most, but not all NFAs studied (Gruszka et al., 2006). Therefore, the basis for sst agonist treatment in NFAs remains weak. However, the recent finding that sst₃ mRNA is expressed in this type of pituitary adenomas (Saveanu et al., 2001b) and the knowledge that sst₃ induces apoptosis by induction of p53 and BAX (Sharma et al., 1996) may reveal a new approach to treatment of NFAs with subtype selective SS analogues.

Gastroenteropancreatic tumours (GEP tumours)

GEP tumours are named *functioning* when they show a clinical syndrome related to hormonal hypersecretion by the tumour and *non-functioning* when no specific syndrome is present and symptoms are only related to the 'mass effect' caused by tumour growth. Hormone peptide and amine hypersecretion may lead to diverse symptom complexes like extensive watery diarrhea, hypokalemia, achlorhydria and hypoglycaemia (Fajans and Vinik, 1989; Long et al., 1981). In sst₂- and sst₅-positive tumours, symptoms related to hypersecretion can be controlled by administration of long-acting SS analogues in around 90% of patients (Arnold et al., 2000; Gorden et al., 1989) and therefore SS analogue therapy is a generally accepted treatment in these tumours. Moreover, tumour shrinkage was observed in a small number of patients receiving standard doses of octreotide (Arnold et al., 1996; Saltz et al., 1993), while in some cases increasing doses translated into significant tumour shrinkage (Anthony et al., 1993; Eriksson et al., 1997; Faiss et al., 1999).

However, SS analogue therapy does not provide a curative treatment regimen, as tumour growth advances in nearly all patients with GEP tumours.

Recently, advances have been made with respect to the treatment of GEP tumours with radiolabeled SS analogues. This application of therapy with radiopharmaceuticals to GEP tumours depends on the concept that coupling of a radioisotope to a molecule which specifically binds to tumour cells could deliver an effective radiation dose to the tumour without damaging healthy tissues, thus limiting adverse effects (Krenning et al., 1999). The development of ¹⁷⁷Lu- tetraazacyclododecanetetraacetic acid (DOTA)-Tyr³-octreotate, which is a β- and γ- emitter and showed highest binding affinities to sst₂ (De Jong et al., 2002), has provided a new molecule for tumour targeted therapy using radiolabeled SS analogues (Kaltsas et al., 2005). ¹⁷⁷Lu-DOTA-Tyr³-octreotate has several advantages compared to other previously developed radiopharmaceuticals, as it can achieve higher absorbed doses for most

tumours, without a change in dose to the dose-limiting organs because of the lower tissue-penetration, a feature particularly important for smaller lesions (de Jong et al., 2003). Recent studies in relatively large study populations have reported complete response in 2-3%, partial response in 26-35%, stable disease in 35-41% and progressive disease in 18-21% of patients treated with ^{177}Lu -DOTA-Tyr³-octreotate (Kwekkeboom et al., 2003; Kwekkeboom et al., 2005a). The same group has recently assessed the effect of ^{177}Lu -DOTA-Tyr³-octreotate therapy on the self-reported Quality of Life (QoL) in patients with metastatic GEP tumours, showing a significant improvement in global health/QoL, as well as several function and symptom scales after ^{177}Lu -DOTA-Tyr³-octreotate therapy, even in patients with progressive disease (Teunissen et al., 2004). These studies suggest a favourable role for treatment of GEP tumours using ^{177}Lu -DOTA-Tyr³-octreotate, also due to the lack of serious side effects (Kwekkeboom et al., 2005a). Another radionuclide of interest is ^{90}Y , a pure high-energy β emitter, which can form a stable complex with the SS analogue (DOTA), Tyr³ octreotide (DOTATOC) (de Jong et al., 1999). In rats with subcutaneous tumours, ^{90}Y -DOTATOC effectively controlled tumor growth (de Jong et al., 2001). Comparison of the characteristics of the β -emitters ^{177}Lu and ^{90}Y shows that each has specific potential advantages for tumour therapy. ^{90}Y particles have higher energies and longer particle ranges, leading to more radioactivity in the tumour cell per peptide molecule and to a better crossfire through the tumour, which is especially advantageous in larger tumours and in tumours with heterogeneous receptor distribution. The shorter half-life of ^{90}Y leads to a higher dose rate. ^{177}Lu particles, on the other hand, have lower energy and smaller particle range, leading to better absorption in smaller tumors. In addition, ^{177}Lu emits γ -radiation with an energy suitable for scintigraphy, enabling dosimetry during PRRT, and also has a longer half-life, making shipping more convenient (de Jong et al., 2005). In pre-clinical studies in rats it was recently demonstrated that combination therapy using both radiolabeled SS analogues resulted in significant better tumour response, compared to a treatment strategy using only one of both compounds (de Jong et al., 2005). Moreover, it was shown that tumour diameter may be of importance in choosing treatment options, the optimal tumour diameter calculated for ^{90}Y being 34 mm and the optimal tumour diameter calculated for ^{177}Lu being 2 mm (de Jong et al., 2005). These findings are in accordance with the different β -energies and particle ranges of ^{90}Y and ^{177}Lu . Future clinical studies will further reveal the significance of combination therapies in GEP tumours. The use of ^{177}Lu -DOTA-Tyr³-octreotate in treatment of GEP tumours seems to be of high value.

Imaging techniques in (neuro)endocrine tumours

The expression of sst subtypes in human (neuro)endocrine tumours of various origins allows in vivo visualization of tumour sites after injection of radionuclide-labeled SS analogues (Krenning et al., 1993; Krenning et al., 1994b; Krenning et al., 2005). ^{111}In -pentetreotide is currently the radiopharmaceutical of choice in visualizing receptors for SS analogues.

Neuroendocrine tumours

In previous studies sst receptor imaging has been shown to be of value in imaging gastrointestinal neuroendocrine tumours and carcinoids (Comaru-Schally and Schally, 2005; Lamberts et al., 2002), with a sensitivity varying from 75 to 95 %. ^{111}In -pentetreotide scintigraphy allows a more accurate staging of the disease, showing sites of disease which were not detected by conventional imaging techniques, visualizing resectable tumours, that would have remained undetected by conventional imaging. It may prevent surgery with curative intent in patients with metastatic disease and it may select patients applicable for treatment with SS analogues or with tumour targeted radioactive treatment using radiolabeled SS analogues (Jamar et al., 1995; Kaltsas et al., 2004; Krenning et al., 1994a; Krenning et al., 1994b; Krenning et al., 2005; Kwekkeboom et al., 2005a; Kwekkeboom et al., 2005b).

Pheochromocytomas

^{123}I -MIBG scintigraphy shows a higher detection rate for benign pheochromocytomas compared to ^{111}In -pentetreotide scintigraphy, however, ^{111}In -pentetreotide scintigraphy may reveal ^{123}I -MIBG scintigraphy negative lesions in malignant pheochromocytomas (Tenenbaum et al., 1995; van der Harst et al., 2001).

Medullary thyroid carcinoma and pituitary adenomas

SS analogues have limited therapeutic value in patients with medullary thyroid carcinoma. Moreover, tumour targeted radioactive treatment using radiolabeled SS analogues seems of

little value as well, due to limited radioactivity uptake by these tumours (Kaltsas et al., 2004). Therefore, there is no role for ^{111}In -pentetreotide scintigraphy in selecting patients for these therapies.

Also in pituitary tumours from different origins ^{111}In -pentetreotide scintigraphy is of very low value. Conflicting results have been published using this technique, showing differences in uptake and a poor correlation to the therapeutic effects of “cold” SS analogues (de Herder et al., 2006).

CST and SS in the human immune system

The expression of SS, CST and sst in the human immune system has been investigated in detail recently (Dalm et al., 2003c; Dalm et al., 2003d; Lichtenauer-Kaligis et al., 2004). First reports on the expression of sst in cells of the human immune system were made by the group of Bhathena and co-workers back in 1981 (Bhathena et al., 1981). They found low-affinity binding sites on resting monocytes and lymphocytes. Using fluorescent SS, sst were identified on mitogen-activated human peripheral lymphocytes (Hiruma et al., 1990). Subsequent studies have characterized the sst subtype expression in cells and tissues of the human immune system in more detail. Table 1 summarizes the distribution pattern of the different sst subtypes in the immune system.

The wide expression of sst subtypes in the human immune system suggests a potential functional significance of SS and its receptors in immune cell function. Expression of SS itself has been investigated in cells of the human immune system, however it was demonstrated that SS expression was restricted to the human thymus, and in the human thymus, only in the thymic epithelial cells and not in the lymphoid component (Ferone et al., 1999). Human monocytes, macrophages, dendritic cells, peripheral blood mononuclear cells, bone marrow and spleen did not show SS expression (Dalm et al., 2003d). Therefore it was suggested that SS may act via the sst expressed on immune cells via the innervating neurons, as lymphoid organs are highly innervated (Stevens-Felten and Bellinger, 1997). The

functional significance of SS in the human immune system remains largely unknown, although different potential effects have been described in previous studies.

Cell proliferation

It is known that ss_{t1} , ss_{t2} , ss_{t4} and ss_{t5} are able to arrest cell growth and thus may contribute to an anti-proliferative effect of SS (Florio et al., 1999; Sharma et al., 1999). On the other hand, ss_{t3} is involved in apoptosis by inducing p53 and BAX (Sharma et al., 1996; Sharma and Srikant, 1998). In recent years both inhibitory (Atiya et al., 1997; Casnici et al., 1997; Lattuada et al., 2007; Payan et al., 1984) and stimulatory (Johansson and Sandberg, 1989; Krantic et al., 1997) effects of SS or its analogues on cell proliferation have been described. Until now it remains unclear which is the functional significance of SS with respect to controlling cell proliferation in human immune cells *in vivo*.

Secretion processes

SS is mainly known for its inhibitory actions on secretion processes, like for instance in the neuroendocrine system (Patel, 1999). In the human immune system SS was found to have a predominant inhibitory effect on secretion of cytokines and immunoglobulins, albeit mainly in studies performed *in vitro* (Fais et al., 1991; Ghamrawy et al., 1999; Kimata et al., 1993; Muscettola and Grasso, 1990; Peluso et al., 1996).

Migratory effects

SS may be a mediator of the regulation of migration of immune cells towards sites of inflammation. SS controls adhesion of T-lymphocytes to fibronectin (Levite et al., 1998), an important glycoprotein of extracellular matrix and, more recently, it has been demonstrated that SS may act as a chemo-attractant to human primitive haematopoietic cells (Oomen et al., 2002). Therefore, SS may play a role in inflammatory processes by directing immune cells towards the sites of inflammation, or SS may play a role in regulation of development of immature immune cells.

As described previously, SS itself is not expressed in cells of the human immune system. Thus, it was hypothesized that SS reaches its receptors in these cells via innervating nerve endings.

However, the recent detection of wide CST expression in cells and tissues of the human immune system (Dalm et al., 2003d) has emerged a completely new field of research. Instead

of SS itself, CST may act via the sst in cells and tissues of the human immune system, thus a CST-sst regulatory circuit may be present in these cells.

In previous studies we demonstrated that CST in the human thymus negatively controlled cell proliferation of thymocytes (unpublished results), comparable to our findings with respect to the effects of SS on thymocytes (Ferone et al., 2002), suggesting a role for CST in selection of cells and thus a regulatory role in mature thymocyte development. We also demonstrated that expression of CST mRNA levels were correlated with levels of activation of various immune cells. During maturation of monocytes into mature macrophages and dendritic cells, CST mRNA levels were upregulated. Stimulation of these cells by lipopolysaccharide (LPS) resulted in upregulation of CST mRNA expression as well (Dalm et al., 2003c). These findings point to a regulatory role for CST in inflammatory processes.

Very recently, the group of Delgado et al. has investigated the role of CST in immune cells during inflammatory processes in more detail in rodent models. In murine models of lethal endotoxemia it was demonstrated that CST prevented the septic shock-associated histopathology, including inflammatory cell infiltration and multiorgan intravascular disseminated coagulation (Gonzalez-Rey et al., 2006a). CST decreased the levels of cytokines, chemokines and acute phase proteins. It was suggested that the main action of CST in regulation in septic shock is deactivation of resident and infiltrating macrophages.

Comparably, in a mouse model for inflammatory bowel disease it was found that CST was able to decrease disease severity, also by decrease in levels of proinflammatory/cytotoxic cytokines, chemokines and acute phase proteins (Gonzalez-Rey et al., 2006c). Finally, the effects of CST were investigated in a murine model for rheumatoid arthritis. CST treatment significantly reduced the severity of collagen-induced arthritis, completely abrogating swelling of joints and destruction of cartilage and bone (Gonzalez-Rey et al., 2006a). CST inhibited the T-helper 1 response and production of proinflammatory cytokines as was previously demonstrated in experimental murine models of endotoxemia and inflammatory bowel disease. These recent findings in murine models imply an important regulatory role for CST in immune-mediated diseases and potential implications for future clinical use. As sst are also widely expressed in affected tissues in patients suffering from immune disease, like rheumatoid arthritis, granulomatous disease (Vanhagen et al., 1994a; Vanhagen et al., 1994b) and inflammatory bowel disease (Reubi et al., 1994) CST may have comparable inhibitory effects in human as well. It may therefore be hypothesized that CST may have future clinical implications in controlling immune cell-mediated disease. However, it should be noted that many differences in sst subtype expression between rodents and human have been described

(Dalm et al., 2003a; Lichtenauer-Kaligis et al., 2000). Differences in sst subtype expression may account for differences in effects between both organisms. Therefore, future in vitro and in vivo studies will be necessary in order to evaluate the functional significance of CST in human immune disease. However, the results in mice are very promising for the future and may present CST as a or one of the factors important in controlling immune disease.

Imaging techniques in diseases of immune-system origin

Lymphomas

Sst have been demonstrated in both Hodgkin's and non-Hodgkin's lymphomas (Lipp et al., 1995; Reubi et al., 1992; Vanhagen et al., 1993). Using in vitro autoradiography studies it was demonstrated that sst are mainly expressed in the lymphoblastic areas of lymphomas, known to be the most active parts of these tumours. In vitro, sst were detected in 70 to 100% of non-Hodgkin lymphomas (Reubi et al., 1992). The detection of sst expression in vitro in lymphomas led to studies using ^{111}In -pentetreotide scintigraphy for detection of sites of disease. Various studies have demonstrated that ^{111}In -pentetreotide scintigraphy shows high sensitivity for detection of affected sites in patients with lymphomas, for a review see: (Dalm et al., 2003b). In general, sensitivity to detect Hodgkin's disease by sst scintigraphy was higher than that for non-Hodgkin's lymphoma. It provided superior results for the detection of supradiaphragmatic localizations, when compared to conventional CT scanning and ultrasonography. Below the diaphragm sst scintigraphy appeared to be less sensitive, due to accumulation of ^{111}In -pentetreotide in liver, spleen, bowel and kidneys. These results may provide a basis for using ^{111}In -pentetreotide scintigraphy in diagnosis and, mainly, staging of lymphomas. Moreover, it would be of great importance if sst scintigraphy could be used for imaging and evaluation of active sites of disease after treatment, providing a tool for follow-up.

Granulomatous disease

Granulomas can be defined as collections of modified macrophages and lymphocytes as a result of the reaction of the host organism to a variety of agents. Fibroblasts and granulocytes may also be present at sites of granuloma formation. They may occur in mycobacterial, parasitic, fungal or other infectious diseases as a reaction to non-infectious, poorly digestible agents and in diseases of obscure origin like Wegener's disease and sarcoidosis. Aggregated granulomas may result in pseudotumour lesions and they may become enclosed by fibrous tissue. Fibrosis may seriously impair for instance lung function and is related to poor prognosis with increased morbidity and mortality. In *Schistosoma mansoni* infection-induced granulomas in mice sst expression has been described (Blum et al., 1992; Elliott and Weinstock, 1996). Following these studies, sst expression was also demonstrated by autoradiography in biopsies of lesions from patients suffering from sarcoidosis (Vanhagen et al., 1994a). In a prospective study the value of sst scintigraphy in granulomatous disease was investigated in a group consisting of 13 patients with sarcoidosis, 4 patients with tuberculosis and 3 patients with Wegener's disease (Vanhagen et al., 1994a). In all patients (20/20) uptake of radioactivity was found by sst scintigraphy. Interestingly, patients with Wegener's disease showed lower uptake of ^{111}In -pentetreotide, which was hypothesized to be due to their pre-treatment with corticosteroids, resulting in a reduction in the size of the granulomatous lesion. However, it cannot be ruled out that the lower uptake of ^{111}In -pentetreotide is due to a down-regulation of sst on the cell membranes, rather than a decrease in the number of affected cells as it is known that glucocorticoids are able to downregulate sst expression (Schonbrunn, 1982). In vitro receptor autoradiography studies confirmed the expression of sst in the region of epithelioid and giant cells of the granulomas. In a second study known mediastinal and hilar lymph nodes, and interstitial lung diseases were detected by sst scintigraphy in 36 out of 37 (97%) patients (Kwekkeboom et al., 1998). Moreover, previously undetected involved sites of

inflammation were detected by sst scintigraphy. Patients were treated and thereafter sst scintigraphy was repeated. In patients, that showed radiological improvement, also a decreased uptake of the radiolabeled somatostatin analogue was found, suggesting that sst scintigraphy might play a role in treatment follow-up. However, because of the small group of treated patients in this study, further prospective studies should be performed to address this question.

Rheumatoid arthritis (RA)

The most characteristic manifestations of rheumatoid arthritis (RA)- joint pain, joint swelling and reduced mobility- are the result of synovitis, an inflammatory process in the synovial tissue. This inflammation leads to joint structure destruction, leading to consequent deformation and loss of function. Van Hagen et al. (Vanhagen et al., 1994b) studied sst scintigraphy in a series of 14 consecutive patients with RA. In all patients uptake of ^{111}In -pentetreotide was observed in at least a number of joints. Lesion-related sensitivity was 74%. It was supposed that the clinical inflammation activity is represented by pain and swelling of the joints. This activity was correlated with the sst scintigraphy results. Recently it was demonstrated by immunohistochemistry that sst₂ was expressed in synovia of affected joints in RA patients (ten Bokum et al., 1999), more specifically on the endothelial cells of venules and on cells of the monocyte/macrophage lineage . Until now, no other studies have been performed evaluating sst scintigraphy in RA. However, this initial study was very promising and larger studies should be performed to further investigate the role of sst scintigraphy in diagnosis of RA. Moreover, Takeba et al. (Takeba et al., 1997) demonstrated that proliferation of RA patients' synovial cells could be inhibited by SS in vitro. In a clinical trial by Paran et al. (Paran et al., 2001), significant clinical improvement was found in patients with active, refractory RA. These results might be the basis for treatment of RA with SS or its analogues. In this respect, the development of the novel SS analogue, SOM-230, is of high interest, as in RA expression of sst_{1,2,3} has been demonstrated (Sakane and Suzuki, 1998). Refractory RA might also be a target for radiotherapy (Kwekkeboom et al., 2000), in which radionuclide-coupled SS analogues are injected in synovia of affected joints. Because of the expression of sst, the radiolabeled SS analogue is internalized in the cells and the radioactivity causes cell death of the infiltrating synoviocytes. This might be particularly important in RA patients that

do not respond to conventional therapies. The role of radiotherapy is currently under investigation.

The role of SS analogue-sst interactions in oncology

Non-neuroendocrine tumours

Besides the wide expression of sst subtypes in neuroendocrine tumours, sst subtype expression has also been described in various other malignancies, like breast cancers, renal cell carcinomas, lymphomas, sarcomas, prostate cancers, hepatocellular carcinomas, colon cancers, gastric cancers and lung cancers (Reubi et al., 2001). Different studies have investigated the potential clinical significance of SS analogues on these tumours as well. The most important expected and interesting effects will be those on cell proliferation in these tumours. Below, we will shortly discuss the current knowledge and fields of research on the differential effects of SS analogues on cell proliferation in various non-neuroendocrine tumours:

Lymphoproliferative tumours

Sst are expressed at affected sites in patients with lymphoma (Dalm et al., 2004a; Reubi et al., 1992). It may be hypothesized that treatment with SS analogues of lymphomas may result in inhibition of cell growth. Until now, only few studies have addressed the question whether lymphomas may be treated with SS analogues in order to control cell growth.

In one clinical trial 61 patients with non-Hodgkin lymphoma (NHL), chronic lymphocytic leukaemia (CLL) and cutaneous T cell lymphoma (CTCL), were treated with octreotide subcutaneously. No patient with CLL achieved partial response (PR), while in 36% of patients with NHL and in 44% of CTCL patients PR was achieved (Witzig et al., 1995), suggesting an anti-proliferative effect of octreotide. The expression of sst in lymphoma tissue is in another prospect, next to the potential direct actions of SS (analogues), of interest in potential treatment strategies. Recently, a cytotoxic SS analogue, AN-238, was developed for the targeted therapy of SS receptor-positive cancers (Nagy et al., 1998). AN-238 consists of the carrier SS octapeptide RC-121 linked covalently to a highly potent derivate of doxorubicin,

AN-201 (Nagy et al., 1996). This analogue binds with high affinity to sst subtypes 2 and 3 and fully retains the cytotoxic activity of the radical. AN-238 was found to inhibit growth of sst-positive experimental tumours (Schally and Nagy, 2003; Schally and Nagy, 2004). AN-238 was evaluated in 2 different human NHL cell lines xenografted in nude mice (Keller et al., 2005). It was demonstrated that AN-238 significantly inhibited tumour growth, while RC-121 and AN-201 itself did not show any effects on tumour size. This suggests that conjugation of AN-201 to RC-121 is essential for its delivery to the sst-positive tumour cells in order to exert its effects. These findings are very promising with regard to future treatment options of lymphomas with cytotoxic targeted SS analogues, but clinical studies have to be performed to evaluate its clinical use.

Breast cancer

Around 85-90 % of human breast tumours are sst positive (Reubi et al., 1990). In experimental studies the SS analogue octreotide has shown to exert anti-proliferative effects on human breast cancer cell lines, with the greatest effects in cells that express sst₂ (Reubi et al., 1990; Weber et al., 1989; Woltering et al., 1997). In a previous study the effects of the SS-analogue RC-160 were evaluated in patients with pre-treated metastatic breast cancer (O'Byrne et al., 1999). No tumour response was observed in this study, suggesting that monotherapy with SS-analogues is of no value in breast cancer treatment. Interestingly, a number of studies have provided evidence for upregulation of estrogen and progesterone receptors on breast cancer cells after stimulation with octreotide, which increases sensitivity of the cells to hormone stimulation (Weckbecker et al., 1992; Weckbecker et al., 1994). Subsequent studies have evaluated the combination therapies on breast cancers. In one study 33 postmenopausal untreated breast cancer women were treated with both lanreotide and tamoxifen (Canobbio et al., 1995). In 50% of patients objective response was achieved (12.5 % CR and 37.5 % PR). However, no control group was studied. In a second study in 22 postmenopausal patients with metastatic breast cancer the effects of tamoxifen alone were compared to the combination therapy with tamoxifen, octreotide and an antiprolactin agent. In the tamoxifen group 36% patients achieved an objective response compared with 55% in the combination therapy group (Bontenbal et al., 1998). Moreover, combination therapy also increased median time to progression. Summarizing the results published so far, SS analogues may play a beneficial role in combination therapy regimens in breast cancers enhancing the effects of antiestrogen therapy. However, in recent years not much progress has been made

and further clinical studies will determine the role for SS analogue co-treatment in this disease.

Prostate cancer

Different studies have addressed the value of SS analogue treatment in prostate cancers. In initial studies no significant effects on tumour growth or symptoms were observed in hormonal-refractory prostate cancers (Figg et al., 1995; Logothetis et al., 1994). One study showed that addition of octreotide to a complete androgen blockade enhanced the rate, quality and duration of symptom-free treatment response, when compared to a control group, solely treated by androgen blockade (Vainas et al., 1997). However, only a small study population was investigated and further clinical studies will be necessary to evaluate the potential clinical significance of SS analogues in prostate cancer treatment regimens.

Small-cell lung cancer

Different studies have been performed using SS analogues as a monotherapy in small-cell lung cancers (Cotto et al., 1994; Macaulay et al., 1991; Marschke et al., 1999). Summarizing these studies, no objective response on tumour growth has been observed. A recent study investigated the effects of the radiolabeled somatostatin analogue [^{177}Lu -DOTA 0 ,Tyr 3]octreotate, which has been used primarily in gastroenteropancreatic neuroendocrine tumors, in a small group of small-cell lung cancer patients (van Essen et al., 2006). Comparable to previous results, no antitumour effects were observed in these patients. Results until now, do not make SS analogues favourable for their use in treatment strategies in small-cell lung cancers.

Gastric cancer

Reports on the use of SS analogues in gastric cancer are limited. In one clinical study (Cascinu et al., 1995) in patients with gastric cancer refractory to chemotherapy treatment, octreotide was compared to best supportive care. Significant improvement in survival was observed with a median survival of 16 weeks in the treatment group, compared to 8 weeks in the supportive care group. In no patients objective response was achieved. In subsequent experimental studies the effects of AN-238 on human gastric carcinomas xenografted in nude mice were evaluated (Szepeshazi et al., 2003). Significant tumour suppression was observed

in the carcinomas positive for sst₂ and sst₅. However, not much new clinical data have emerged and the role of SS analogues in gastric cancer remains unclear.

Colorectal cancer

Octreotide was shown to inhibit growth of experimental colorectal tumours both in vitro and in vivo, which may be explained by its antiangiogenic properties (El-Salhy and Dennerqvist, 2004; Melen-Mucha et al., 2000). Patients who were planned to undergo surgery were given octreotide for 2 weeks before surgery, which led to a significant reduction in VEGF-levels, which is a major angiogenic growth factor (Cascinu et al., 2001b). The potential beneficial effects of this pre-treatment include a presurgical reduction in tumour viability, tumour volume and tumour vascularization. In 2 clinical studies the role of SS analogue treatment was found to be very limited (Cascinu et al., 1995; Goldberg et al., 1995). In the first study no objective response was achieved, although median survival time was 24 weeks in the treatment group and 12 weeks in the untreated control group (Cascinu et al., 1995). In the second study no beneficial effects were found on tumour size or survival (Goldberg et al., 1995). The role for SS analogues in colorectal cancers therefore seems to be limited. Possibly, it may play a role in presurgical preparation, in order to increase the success rate of surgery, however data are still limited.

Hepatocellular carcinoma

In a clinical studies in 58 patients with advanced hepatocellular carcinoma treatment with octreotide was compared to no treatment (Kouroumalis et al., 1998). Treated patients were found to have a higher median survival with 13 months compared to 4 months in the untreated group. In a second comparable study in 28 patients median survival was 31 weeks in the 15 patients receiving octreotide and 16 weeks in the 13 patients receiving no treatment (Dimitroulopoulos et al., 2002). Very recent studies in larger populations have not demonstrated effects of octreotide on median survival (Becker et al., 2007) or anticancer activity (Cebon, 2006). The role for SS analogues in these diseases therefore seem to be of little importance. Potential antitumour activities of SS analogues may be expected in combination with chemotherapy. Experimental studies demonstrated that octreotide showed antiangiogenic activity and inhibited growth of tumour in human hepatocellular carcinoma xenografts (Jia et al., 2003). It may therefore be hypothesized that octreotide may be used in

an adjuvant or neoadjuvant setting in combination with chemotherapy. However, additional studies are needed.

Pancreatic cancer

In clinical trials the role of SS analogues has been investigated in patients with advanced irresectable pancreatic cancer in phase I and II clinical trials (Poston and Schally, 1993; Schally et al., 1994). Patients were treated with different doses of octreotide. In both studies 30% of patients showed tumour stabilization by CT for 6 months with measurable improvement of quality of life. In a study by Rosenberg et al. (Rosenberg et al., 1995), treatment with tamoxifen was combined with octreotide and compared to a cohort of untreated patients. Median survival in the treatment group was 12 months, while in the untreated group only 3 months. Various other studies have addressed the question whether treatment of pancreatic cancers with octreotide alone or in combination with tamoxifen or LH-RH antagonist may be of benefit (Canobbio et al., 1992; Fazeney et al., 1997; Friess et al., 1993; Klijn et al., 1990; Reubi et al., 1988; Sulkowski et al., 1999). Summarizing these studies, no objective beneficial effects of treatment with octreotide were found on tumour progression or survival, however in individual cases improvement in quality of life was observed. Cascinu et al. therefore concluded that, although octreotide seems not to be of influence on tumour progression, further studies will reveal the potential effects of octreotide treatment in chemotherapy refractory patients on quality of life (Cascinu et al., 2001a). An explanation for the lack of effects of SS analogue therapy may be the lack of sst. Previous studies showed a loss of sst₂ gene expression in pancreatic carcinomas, when compared to normal pancreatic tissue (Buscail, 1998; Buscail et al., 1996), which is the preferential target for the classical octapeptide SS analogues. Therefore, the role of SS analogues in treatment of these diseases seems to be limited.

Summary, discussion and conclusion

In recent years, the role of SS analogue therapy in neuroendocrine disorders has well been established, being the first choice of treatment in acromegaly (Lamberts et al., 1996) and being of great value in controlling symptoms in GEP carcinomas (Oberg et al., 2004). The recent development of new, more receptor subtype specific or multiligand SS analogues has

increased the potential indications for their use in clinical practice. Due to differences in sst subtype expression patterns between patients with the same disorders, new SS analogues may have more potent effects when compared to the widely used sst₂-specific SS analogues. Acromegalic patients not responsive to the more sst₂-selective octreotide may therefore respond to SOM230 (Hofland et al., 2004; Murray et al., 2004; van der Hoek et al., 2004). Cushing's disease may now also become a target for sst-agonist treatment, due to expression of sst₅ (Hofland et al., 2005; van der Hoek et al., 2005). The role of sst-agonist treatment in other pituitary adenomas, like TSH-secreting and prolactinomas remains to be determined, although recent studies suggested potential beneficial effects of sst-specific analogues in these diseases (Chanson et al., 1993; Comi et al., 1987; Grottoli et al., 2006; Hofland et al., 2004; Horiguchi et al., 2007; Rubinfeld et al., 2006). Improved knowledge on sst subtype specific modes of action will potentially lead to the introduction of SS-analogue therapy in other pituitary adenomas than acromegaly alone. Major progress has been made in SS-analogue treatment modalities in GEP tumours. First "cold" SS-analogues were used for symptom control, but with the introduction of tumour targeted radioactive labelled SS-analogue therapy it was demonstrated that also effects on the tumour itself could be achieved, while adverse effects of therapy were very little (Kwekkeboom et al., 2003; Kwekkeboom et al., 2005a; Kwekkeboom et al., 2005b; Teunissen et al., 2004). Further studies will be performed in order to define clinical implications for this treatment modality in other neuroendocrine tumours as well. In oncology, the use of SS analogue therapy seems very limited until now. In vitro studies in lymphomas a favourable role for AN-238, a cytotoxic SS analogue, was found in inhibiting tumour growth (Keller et al., 2005; Nagy et al., 1996; Nagy et al., 1998; Schally and Nagy, 2003; Schally and Nagy, 2004). In vivo studies will have to determine the clinical significance of these findings. In other oncologic diseases, only small studies are available and until now no beneficial effects for SS analogue treatment were observed, although some studies may seem promising in combining SS-analogue therapy with other treatment modalities. This should be studied further in more detail.

Recently, the detection of CST has led to new fields of research. In neuroendocrine systems, CST seems to play a regulatory role, comparable to that of SS. However, in the human immune system, which lacks SS, CST was found to have a major beneficial effects in controlling auto-immune and inflammatory processes (Gonzalez-Rey et al., 2006a; Gonzalez-Rey et al., 2006b; Gonzalez-Rey et al., 2006c), although all studies showing these effects were performed in mice, of which we know that sst subtype expression pattern may be

different from that in human immune cells. Further clinical studies will have to show whether CST may also exert these promising effects in controlling inflammatory diseases in human both in vivo and in vitro. Furthermore, in immune-mediated disease the role of radioactive labelled SS analogues in visualization of affected sites, as already generally accepted in neuroendocrine disorders, is of interest, for instance in staging and follow-up in diseases as lymphomas, granulomatous disease and RA. Until now only small studies have addressed this topic and as results seem promising (Vanhagen et al., 1994a; Vanhagen et al., 1993; Vanhagen et al., 1994b), further clinical studies need to be performed.

The recent observation that sst are able to form homo- and heterodimers (Pfeiffer et al., 2001; Pfeiffer et al., 2002; Rocheville et al., 2000) may also have clinical consequences. Homo- and heterodimerization can alter the functional properties of the receptors with respect to ligand binding, desensitization, internalization and upregulation. For example, bi-selective sst agonists may have preferential effects over mono-selective sst agonists in treatment modalities. The significance of sst dimerization is currently still under investigation.

Finally, some final thoughts remain with respect to studies performed towards SS/CST and sst interactions in animal, mainly murine, models. First, it has been previously demonstrated that expression patterns of sst subtypes, SS and CST differ between rodents and human in the various organ systems. Therefore, results obtained in animal models should be translated to situations in human with a certain caution, as these may significantly differ between the different species. Secondly, studies in SS- and CST knock-out mice have shown that these animals may function without developing major problems. This may suggest that other SS-like peptides, next to the recently discovered CST, may be responsible for the SS-like actions in these animals. As not much is known about these situations in human, also results in these knock-out models should be interpreted with caution. Further studies will reveal whether the results obtained in these models can be extrapolated to human.

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