The efficacy of somatostatin analogues in the treatment of diabetic retinopathy and thyroid eye disease

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Abstract: Somatostatin, a polypeptide hormone of 14 or 28 aminoacids, is produced by neuroendocrine, inflammatory and immune cells. It has multiple inhibitory functions on the secretion of various hormones and growth factors and modulates several cellular functions. Somatostatin analogues provide an elegant pharmacological principal to modify the high-risk form of proliferative diabetic retinopathy. Pilot investigations have provided evidence that octreotide can very effectively suppress new bleeding and stop visual loss in patients who have failed conventional photocoagulation therapy. In this cohort, octreotide was found to be a safe treatment modality. The same applies also for thyroid eye disease, in which some non-randomized, as well as randomized studies have shown a beneficial effect. More potent analogues, like SOM230, which are not yet in the market, can be proved to have a better therapeutic outcome in such patients and may be considered a safe treatment modality to stop the progression from pre-proliferative to proliferative diabetic retinopathy. This is also true for adolescent patients with thyroid eye disease, as well as for adults who also suffer from diabetes mellitus.

Keywords: thyroid eye disease, diabetes mellitus, diabetic retinopathy, somatostatin analogues, octreotide

Introduction

Progressive damage to the eyes, kidneys, nerves and large vessels represents the major threat to health and life of diabetic patients. Therefore, prevention of complications should be the main target in these patients. Retinopathy is the most frequent and specific chronic microvascular complication of diabetes mellitus (DM). It represents a major threat to eyesight in the west and is the main cause of blindness among people of working age (Kohner 1993). In fact, early signs of retinopathy are apparent in all individuals with type 1 diabetes after 20 years and in about 80% of those with type 2 diabetes of similar duration (Klein et al 1984a, 1984b). It is characterized by the loss of pericytes, hypertrophy of basement membrane, microaneurysms formation, increased vascular permeability, capillary occlusions, neovascularization and fibrovascular proliferation. The pathogenesis of diabetic retinopathy (DR) is still insufficiently understood, although some reports have implicated the role of the immune system. The finding of antipericyte and antiendothelial cell autoantibodies in the circulation of diabetic patients strongly suggests that some autoimmune activity has been involved in the early pathophysiology of DR. There is even more evidence that implicates the presence of autoimmune mechanisms in the proliferative stage of the disease, such as increased vitreous concentration of the interleukin-6 and interleukin-8 in patients with proliferative retinopathy (Yuuki et al 2001; Kastelan et al 2007).

In diabetic patients, human leukocyte HLA class II DR and DQ antigen expression on the retinal vascular endothelial cells, as well as on pigment and nonpigment

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epithelial cells, was found. These antigens are normally restricted to immunocompetent cells and play an important regulatory role in the immune response. Abnormal expression of DR and DQ antigens at sites where they do not normally exist would result in autoimmunity by converting the target cell into a functional antigen – presenting cell. In conclusion, there is increasing evidence of the presence of some autoimmune processes in the early stages of diabetic retinopathy and particularly in its proliferative phases and it may be considered as an autoimmune disease (Kastelan et al 2007).

Thyroid-associated ophthalmopathy (TAO) or thyroid eye disease (TED) is an autoimmune disease and refers to the eye changes observed in Graves' disease (GD). The orbital involvement is characterized by lymphocytic infiltration and edema of retrobulbar tissues, resulting in marked swelling of extraocular muscles and orbital fat. Due to the increased volume of orbital contents the retrobulbar pressure rises, interfering with venous drainage (causing lid swelling) and pushing the globe forwards (causing proptosis or exophthalmos) (Bahn and Heufelder 1993; Krassas and Heufelder 2001). In severe cases direct pressure on the optic nerve may result in loss of visual functions. The swelling of eye muscles hampers muscle motility, associated with double vision. The swelling of retrobulbar tissues is largely attributable to excessive secretion of glycosaminoglycans (GAGs) by orbital fibroblasts (OFs). In vitro studies have shown that OFs are capable of producing GAGs in response to various cytokines. These cytokines are probably released by infiltrating T-lymphocytes in the orbit. Accumulating data have led to widely accepted view that the OFs are the primary targets of the autoimmune attack. Regarding the nature of the autoantigen consensus has now been reached that the full-length thyrotropin stimulating hormone (TSH) receptor (TSH-R) is expressed at the messenger RNA and protein level in orbital adipose/connective specimens of TED patients but scarcely in that of controls (Krassas 2005). The TSH-R is functional, as evident from an increase of cAMP in response to TSH. Overall, the preponderant concept regarding the nature of the autoantigen is that a subpopulation of OFs may be the target cells in TED, enabling the preadipocytes, when stimulated, to differentiate into nature adipocytes expressing increased levels of TSH-R (Krassas and Wiersinga 2005). Recently, they have been identified several other key antigens namely, flavoprotein (FP), G2s, and the calcium binding protein calsequesterin (CSQ). It turns out the CSQ is expressed 4.6 times more in extraocular muscle than in other skeletal muscle, which may partly explain the specificity of the skeletal muscle reactions in GD in the orbit (Gopinath et al 2006).

Recent studies have shown that antibodies against CSQ are specific and sensitive markers for eye muscle damage in patients with TAO. CSQ antibodies are also markers of chronic upper eyelid retraction in patients with GD, Hashimoto thyroiditis and transient thyroiditis. Antibodies targeting the orbital fibroblast cell membrane protein collagen XIII are linked to the "congestive ophthalmopathy" subtype of TAO whereas, in seminal case studies, TSH-R antibodies bear no relationship with eye signs. These recent findings may represent an important breakthrough in our understanding of ophthalmopathy and may provide reliable clinical tests for diagnosis and management purposes (De Bellis et al 2005; Gopinath et al 2006).

In summary, TED is an autoimmune disease in which the nature of all the autoantigens involved in the autoimmune process has not yet been identified. TSH-R plays a key role, enabling the preadipocytes to be differentiated into mature adipocytes. Regarding DR, although the pathogenesis is not completely understood, it is known that the immune system certainly involved in its development, which may be the link between the two diseases. The connective tissue inflammation in the retina and the periorbital space would be a common target of SM-as.

The incidence of TED varies among different studies. The most accurate data on the incidence of TED is derived from a population-based cohort study in Olmsted County, Minn, USA (Bartley et al 1995). The overall age-adjusted incidence rate was 16.0 cases for women and 2.9 cases for men per 100,000 population per year. Peak incidence rates were observed in the age groups 40–49 and 60–69 years. The incidence rates start to increase from the age of 20 years. Only 6 out of the 120 incident cases of TED observed in this cohort study were in patients below the age of 20 years.

SM-as have been used so far in uncontrolled and controlled randomized studies in the treatment of diabetic retinopathy (DR) and TED, in different doses. Some studies reported encouraging results (Krassas 2001, 2004; Krassas and Boboridis 2006).

The aim of this review is to present all new information regarding the use of SM-as in the treatment of these two appalling diseases and also provide evidence regarding the future role of pharmacotherapy in the progression of DR and TED.

Somatostatin and somatostatin receptors

Somatostatin (SM) is a polypeptide hormone of 14 (SST-14) or 28 (SST-28) amino acids produced by neuroendocrine, inflammatory and immune cells (Patel 1999). It is synthesized as 116-long aminoacid precursor called preprosomatostatin that is cleaved by a protease to the prohormone prosomatostatin (92 aminoacid long) and finally by endoproteolytic processing to the 14 or 28-aminoacid peptide SM (Dasgupta 2004). It has multiple inhibitory functions on the secretion of various hormones and growth factors and modulates several cellular functions (Table 1) (Siler et al 1974; Unger et al 1978; Bueno and Ferre 1982; Krejs 1986; Thorner et al 1990; Makhlouf and Schubert 1990; Lewin 1992; Epelbaum et al 1994; Lauder et al 1997; Bruns et al 2000; Ferjoux et al 2000; Dasgupta 2004).

The biological functions of SM are mediated through somatostatin receptors (SMRs), an evolutionary conserved receptor system (82%–96% homology between humans and rodents). SMRs are high-affinity G-protein coupled receptors expressed in target cells (Patel 1999). There are five functional somatostatin receptors (SMR1-5), and SMR2 has two forms, SMR2A and SMR2B, generated by alternative splicing in the cytoplasmic tail (SMR2 is the only SMR that has an intron) (Reisine and Bell 1995). Ligand (somatostatin) -binding leads to receptor phosphorylation (Liu 2003), G-coupled protein activation and receptor internalization (Hofland and Lamberts 2003).

Signal transduction downstream somatostatin receptors

All 5 SMR subtypes signal though pertussis toxin-sensitive G-protein coupling that leads to inhibition of adenyl cyclase and lowering of the intracellular c-AMP levels (Lewin 1986; Strnad et al 1993). There is also evidence that SMR1, SMR2 and SMR5 stimulate phospholipase C (PLC) that leads to increased calcium mobilization, SMR1 inhibits the Na+/H+ exchanger, SMR1, SMR2, SMR3 and SMR4 activate protein tyrosine phosphatases, SMR1, SMR3, SMR4 and SMR5 downregulate the MAPK/ERK pathway and finally, SMR4 leads to STAT3 phosphorylation and nuclear translocation (Dasgupta 2004). Consequently, there is an extremely complex signal transduction network that is influenced by SM and the final outcome may rely 1st) on the concentration of the hormone (SM), 2nd) on the differential expression of SMR subtypes on the target cell, and 3rd) on the coupling of signal transduction pathways to the receptors and their crosstalk in each cell type.

Therapeutic approach to diabetic retinopathy and thyroid eye disease using SM-as

Diabetic retinopathy

Various SM-as have been developed and used in clinical practice because the short half-life of SM makes it unsuitable for routine treatment (Croxen et al 2004). In the last fifteen years it has been shown that SM-as might be of therapeutic value in the treatment of DR and TED.

Table 2 summarizes the studies published so far, in which SM-as have been used in the context of DR. Some studies reported effects on the suppression of growth hormone levels, stabilization of neovascularizations, resorption of hemorrhages and the reduction in the number of microaneurysms. In a case report, effective treatment of a macular edema was also reported (Kuijpers et al 1998).

Table 1 Physiological functions of somatostatin

Function	Ref
Regulation of hormone secretion	
Growth hormone	Thorner et al 1990
TSH	Siler et al 1974
Insulin	Unger 1978
Glucagon	Unger 1978
Gastro-intestinal functions	Lewin 1992
Inhibition of gastric acid secretion	Makhlouf and Schubert 1990
Inhibition of intestinal motility	Bueno and Ferre 1982
Inhibition of absorption of nutritients and ions	Krejs 1986
Vascular effects	
Inhibition of vascular contractility	Lauder et al 1997
Inhibition of vascular remodeling	Bruns et al 2000
Inhibition of angiogenesis	Dasgupta 2004
Inhibition of cellular proliferation	Dasgupta 2004
Neurotransmitter	Epelbaum et al 1994
Modulation of signal transduction and gene expression	Ferjoux et al 2000

Table 2 Clinical studies in diabetic retinopathy using octreotide (adapted from Reisine and Bell 1995)

Reference	Stage of DR	Diabetic patient numbers and controls	Treatment	Study duration
Kirkegaard et al (1990)	Early diabetic retinopathy	11 IDDM 9 controls 7 pts and 7 controls completed the study	Octreotide Continuous sc infusion (up to 400 μg/day)	1 year
Mallet et al (1992)	PDR progressing despite photocoagulation	4 IDDM no controls	Octreotide Continuous sc infusion (400 μg/day) Treatment discontinued by decreasing dose by 100 μg every month.	15 months (mean) (6–20 months)
Efthymiou et al (1995)	PDR	2 diabetic patients	Octreotide SC 100 μgx3/d	3 months
Grant et al (1996)	Severe non-proliferative DR, non-high risk PDR	16 pts (8 pts: treated 8 pts: controls)	Octreotide 600–3000 μg/day. Continuous infusion or sc injection	15 months
Grant et al (2000)	Severe non-proliferative DR, early non-high risk PDR	23 pts (11 pts: treated 12 pts: controls)	Octreotide 11 pts: 200–5,000 μg/day sc 12 pts: conventional diabetic treatment. 11 treated patients and 7/12 control patients given thyroxine replacement.	15 months
Boehm et al (2001)	High-risk PDR, after photocoagulation.	9 patients (5 IDDM, 4 NIDDM) 9 controls (3 IDDM, 6 NIDDM)	Octreotide Sc injection 100 μg tid	3 years

In an uncontrolled trial, Mallet et al (1992) reported beneficial effects of octreotide (OCT) on the retina as regards neovascularization in 4 patients with severe proliferative DR. Kirkegaard et al (1990) investigated the possible beneficial effect of OCT treatment in patients with earlier phases of retinopathy. They didn't find any difference between patients and controls and suggested that perhaps the rate of spontaneous progression in early retinopathy is too low to reveal a beneficial effect of OCT with a one-year study period. In one uncontrolled study Grant et al (1996) reported that OCT did not prevent progression of DR in a trial that included severe non-proliferative and "non-high risk" proliferative DR patients.

In their second controlled (Grant et al 2000) study the same authors studied patients with severe non-proliferative DR or early non-high-risk proliferative retinopathy. At this stage of DR the likelihood for the need of panretinal photocoagulation is high. The SM-as was titrated in 11 patients to the maximally tolerated dose for a 15-month period. Doses of 200 μg/day up to 5000 μg/day of OCT were used. Only one of 22 eyes of the OCT group required panretinal photocoagulation, whereas 9 of 24 eyes in the control group had to be later treated. The incidence of ocular disease progression was only 27% in patients treated with OCT compared with 42% in patients with conventional treatment. This study provided evidence that OCT treatment retarted progression of advanced retinopathy and delayed the time for laser photocoagulation (Grant et al 2000).

In another controlled study, Boehm et al (2001) reported the use of OCT in a cohort of diabetic patients with a very advanced stage of proliferative DR ie, presence of active proliferations after a full scatter laser treatment (Boehm et al 2001).

Table 3 The initial clinical studies in TED using OCT (reproduced from Krassas 2004)

Reference	Type of analog	No. of patients studied	respondents
Chang et al (1992)	Octreotide	6	6
Krassas et al (1995)	Octreotide	12	7
Ozata et al (1996)	Octreotide	10	5
Khoo et al (1995)	Octreotide	8	6
Kung et al (1996)	Octreotide	8	6
Uysal et al (1999)	Octreotide	9	7
Durak et al (1995)	Octreotide	3	0
Krassas et al (1997)	Lanreotide	5	4
Krassas et al (1997)	Lanreotide	5	4
	Octreotide	5	4
Krassas et al (2001)	Long-acting release octreotide	2	2
Total		73	51

A dose of 300 μg/day of OCT was used in 9 patients; 9 patients with standard diabetes management served as controls. The observation period was the longest ever reported in a trial using a SM-analogue for the treatment of DR. After 3 years of treatment the incidence of vitreous hemorrhages was significantly lower in the OCT-treated patients. Also, visual acuity was preserved and significantly better over time in the OCT-treated group. Only in the OCT group did a regression of proliferations occur, as defined by stereoscopic photography and angiography (Boehm et al 2001). There were no severe side effects or hypoglycemic events. There are also some case reports, which have demonstrated that SM-as inhibit vascular effusions (Kuijpers et al 1998; van Hagen et al 2000).

Thyroid eye disease

In the last decade it has also been shown, that SM-as might be of therapeutic value in the treatment of active TED in adults. Table 3 depicts the initial clinical studies in TED using OCT. Most of these studies were uncontrolled, not randomized and included only small number of patients (Krassas 2004).

In the past 2 years, four double-blind, placebo-controlled clinical studies have been published. In the first (Dickinson et al 2004), 50 euthyroid patients (11 males, 39 females, age 22–74 years, median 50 years) with active TED (CAS $\geq$ 3, NOSPECS 2a–5a, of median duration 0.9 years) received either 30 g LAR or placeboevery 4 weeks for 16 weeks. Both groups then received 30 g LAR for weeks 16–32 and were followed-up without treatment for a further 24 weeks. Objective assessments included all individual parameters of TED, CAS, and derived scores for soft tissue inflammation (STI) and ophthalmopathy index (OI). During weeks 0–16 there was significant reduction in STI, subjective diplopia, and CAS in LAR-treated patients; STI and CAS were also reduced with placebo. The OI reduced by −1.12 in the LAR group ($p = 0.0017$) versus −0.23 with placebo ($p = 0.33$), giving a barely significant treatment effect by Wilcoxon's rank sum test ($p = 0.043$), but analysis of covariance failed to confirm this ($p = 0.16$). During weeks 16–32 there was no significant change in OI in either group. The overall results (weeks 0–32) showed reduction in STI and CAS in both groups. They concluded that no significant therapeutic effect of octreotide LAR was seen in patients with moderately severe TED. The improvement in both treated and placebo groups emphasizes that the results of open studies must be viewed with caution.

In another study of a long-acting SM-a (16 weeks of long-acting release formulation of octreotide [octreotide-LAR]), which was conducted in 51 patients with mild active TED and aimed at preventing deterioration and precluding the need for more aggressive therapeutic modalities, such as glucocorticoids or radiotherapy, no treatment effect was observed for the primary end point (Wemeau et al 2005). The CAS was reduced for patients treated with octreotide-LAR, but without any significant difference from the patients receiving placebo. However, octreotide-LAR significantly reduced proptosis (as measured by exophthalmometry). This was associated with non-significant differences in favor of octreotide-LAR in a series of proptosis-related parameters. These included class III grade, opening of the upper eyelid, the difference in ocular pressure before primary position and upgaze, and extraocular muscle involvement. Evaluating the extraocular muscle volume by magnetic resonance imaging showed a non-significant reduction. No significant correlation between the initial uptake of octreoscan and the response to treatment was observed.

The inference was that in this study, octreotide-LAR did not seem suitable to mitigate activity in mild TED. However proptosis, one of the most debilitating symptoms of TED, was

significantly reduced. The sustained effect on proptosis of just 16 weeks of octreotide-LAR treatment is an encouraging preliminary result in light of the serious lack of therapeutic options for this condition.

Very recently a third similar study was published in which lanreotide 20 mg every two weeks was used in a randomized fashion. A total of 60 patients were investigated. The inference was that lanreotide had no effect on CAS in patients with TED (Chang and Liao 2006).

Finally, one similar randomized, controlled study from the Endocrinology Department of Mayo Clinic, Rochester, MN, USA has just been published (Stan et al 2006). They investigated 29 patients with moderately severe TED. Patients received 4 monthly doses of either octreotide LAR (20 mg) or saline by im injections. The inference was that CAS improved to a greater extend in octreotide-LAR-treated patients than the control group. However, this finding may not represent clinical benefit because patients with higher baseline CAS were overrepresented in the treatment group and the control group was small. In contrast, treatment-related improvement in eyelid fissure width was noted, suggesting that octreotide LAR may be useful in the treatment of a subgroup of active thyroid ophthalmopathy patients with significant lid retraction (Stan et al 2006).

Future perspectives of SM-as in the treatment of diabetic retinopathy and thyroid eye disease

SM-as provide an elegant pharmacological principle to modify the high-risk form of proliferative DR (Aiello et al 1995). The potential role of these substances may be due to suppression of pro-angiogenic molecules, a direct inhibition of pro-angiogenic signaling at the cell level, an anti-fibrotic action, thus reducing fibrovascular formations, and at least a partial correction of the systemic GH and IGF-I dysregulation (Boehm and Lustig 2002). Data from the Boehm study and from other pilot investigations have provided evidence that OCT can very effectively suppress new bleeding and stop visual loss in patients who have failed conventional photocoagulation therapy (Boehm and Lustig 2002). In this cohort, OCT was found to be a safe treatment modality. It remains to be clarified whether the progression from pre-proliferative to proliferative retinopathy can also be stopped by the use of today available SM-a or by the use of more potent analogues like SOM230, which are not yet available in the market. The latter has, in contrast with the so far used analogues, a rather high affinity for all sst subtypes except ss4 (Table 4) (Bruns et al 2002; Croxen et al 2004).

Table 4 Selectivity of somatostatin analogues (adapted from Strnad et al 1993)

	Sst1	Sst2	Sst3	Sst4	Sst5
Somatostatin-14	+	+	+	+	+
Somatostatin-28	+	+	+	+	+
Octreotide		+ (0.6)	+/– (34.5)		+ (7)
MK 678		+			
L779976		+			
L796778			+		
SOM230	+	+	+		+

Binding affinities for octreotide, in brackets, represent IC_{50} values (nM)

The same applies also for TED in which more potent analogues can also proved to be the treatment of choice in moderately severe cases with DM, as well as in adolescents.

It is thus plausible to assume that SOM230 might be much more effective in the treatment of DR and TED.

Clinical research is needed to demonstrate the efficacy of new SM-as in the treatment of DR and TED. Such studies will be proved to be of extremely importance in the pharmacotherapy of these two deliberating diseases.

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