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Use of Somatostatin Analogues in Obesity

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Abstract

Obesity is a condition that results from dysregulation of energy balance. Insulin, a component of the efferent pathway of the energy-regulatory circuit, promotes storage of energy substrates in adipose tissue and is, therefore, a potential target for pharmacotherapy. Somatostatin and its analogues (octreotide and lanreotide) bind to somatostatin subtype 5 receptors on the β-cell membrane, which limits insulin release and, consequently, may decrease adipogenesis. Somatostatin and its analogues have been used in trials in patients with paediatric hypothalamic obesity. These children have hypothalamic dysfunction, mainly due to brain tumours such as craniopharyngiomas, which are thought to generate increased vagal output, leading to hyperinsulinaemia and weight gain. Two small trials, each of 6 months' duration, in children with paediatric hypothalamic obesity showed either a minimal weight loss or stabilization of bodyweight. In children with Prader-Willi syndrome, the most common genetic hypothalamic disorder associated with hyperphagia, hyperghrelinaemia, massive obesity and other endocrine disturbances, somatostatin failed to control hyperphagia and weight gain in a small number of patients, although it lowered the levels of the anorexigenic hormone ghrelin. Long-acting release octreotide was recently used in hyperinsulinaemic obese adults without cranial pathology. Insulin suppression was associated with small decreases in the body mass indexes of obese subjects receiving the higher dosages of the drug, with an acceptable safety profile, similar to that in previous studies. In conclusion, somatostatin and its analogues, by suppressing β-cell insulin secretion, can retard weight gain in children with

hypothalamic obesity and induce a small amount of weight loss in some adults with hyperinsulinaemic obesity.

Obesity is a major health concern with multiple aetiologies and is associated with important adverse medical, psychosocial and economic consequences. It is a growing problem in all age groups, most social classes and ethnic groups.[1,2] Treatment of obesity, especially on a long-term scale, using strategies such as diet, exercise, behavioural therapy and drugs is only modestly effective. Currently, the most successful treatment for obesity is gastric bypass surgery; however, this procedure carries significant risk. The realization that obesity is a chronic disease has led to wider acceptance of the use of drugs for its treatment. At present, only very few drugs are approved for weight reduction.[3] New anti-obesity compounds are currently under development. These drugs can modulate energy homeostasis by stimulating catabolic pathways or inhibiting anabolic pathways.[4]

Somatostatin is a 14- or 28-amino-acid peptide hormone initially isolated in hypothalamic tissue as a suppressor of growth hormone (GH) secretion.[5] The effects of somatostatin are primarily inhibitory and are mediated via somatostatin receptors, which belong to the superfamily of G-protein-coupled receptors.[6] Somatostatin and its receptors can be found throughout the brain, spinal cord and gastrointestinal tract. Five somatostatin receptor subtypes have been cloned and characterized, and were codenamed $SST_{1–5}$.[6] The five receptor subtypes have a tissue-specific distribution and the majority of somatostatin target tissues express multiple receptor subtypes. Several studies have indicated that the somatostatin SST_2 receptor mediates the inhibition of glucagon release from pancreatic α cells, gastrin and gastric acid, as well prolactin secretion, whereas the SST_5 receptor regulates insulin release from β cells.[6,7] Currently available somatostatin analogues (octreotide and lanreotide) bind with an intermediate to high affinity to the SST_2, SST_3 and SST_5 receptors, which belong to the class 1 somatostatin receptor family, but these analogues do not show significant binding to the SST_1 and SST_4 receptors (i.e. the class 2 somatostatin receptor family).[6,8] New potent somatostatin analogues, such as pasireotide (SOM230), show a rather high affinity profile for all somatostatin receptor subtypes except the SST_4 receptor.[9]

Analogues of somatostatin play an important role in the detection and therapy of neuroendocrine disorders, including GH-secreting pituitary adenomas and gastroenteropancreatic tumours.[10] They are used for the treatment of two major indications: acromegaly and carcinoid syndrome. They have also been tested in other disorders, such as thyroid eye disease and diabetic retinopathy, but the results are still controversial and these drugs have not been approved officially for these indications.[11] The synthetic analogues were developed because natural somatostatin has a short half-life of only 1.5–3 minutes.[12]

Obesity is frequently associated with hyperinsulinaemia, both under fasting conditions and postprandially. Insulin produced by pancreatic β cells acts in the CNS as a potent anorexigenic hormone on a long-term basis, and insulin receptors are widely expressed in appetite-controlling areas of the brain.[13] Both insulin and leptin are secreted in the bloodstream in proportion to the amount of body fat of the individual, and they function as adiposity signals by interacting with target neurons, mainly in the hypothalamus, to repress food intake.[14] Insulin is also a major component of the efferent pathway of energy balance and, in contrast to its central anorexigenic action, promotes storage of energy substrates in adipose tissue and adipogenesis. Therefore, insulin suppression is a potential target for obesity pharmacotherapy.[15] Several studies have shown that somatostatin and its analogues may limit insulin release by binding to the SST_5 receptor on the β-cell membrane and, consequently, decrease adipogenesis and weight gain.[16,17] Some clinical trials, both in children and adults, have recently examined the

possible usefulness of the administration of somatostatin analogues in hyperinsulinaemic obesity.[18-20]

In this review, we examine the rationale (pathophysiology and mechanisms) of the role of somatostatin in obesity; the efficacy and safety of somatostatin analogues in paediatric hypothalamic obesity, with special emphasis on Prader-Willi syndrome (PWS); and finally, its use in hyperinsulinaemic obesity in adults.

1. Rationale for the Use of Somatostatin Analogues in Obesity

Increased insulin secretion and insulin resistance are characteristic features of human abdominal obesity.[21] It is usually assumed that the hyperinsulinaemia found in obese subjects is secondary to their insulin resistance, but some evidence suggests that hyperinsulinaemia *per se* may lead to some forms of obesity.[22] Indeed, an exaggerated first-phase insulin response to intravenous glucose has been shown to predict future weight gain.[23] Similarly, in children, an increased early postprandial insulin response seems to play a major role in the development of obesity.[24] Additionally, sensitivity to the anti-lipolytic action of insulin is maintained in obese individuals, in contrast to the development of resistance to the glycoregulatory action of insulin, as demonstrated by euglycaemic clamp studies.[25] This concept is supported by the experimental observation that adipocytes show little resistance to insulin inhibition of lipolysis.[26] These studies suggest that insulin hypersecretion may be a risk factor for obesity, whereas reducing hyperinsulinaemia would be expected to reverse obesity. Insulin promotes adipogenesis by stimulating the activity of adipose tissue lipoprotein lipase, which, in turn, promotes the partitioning of ingested energy substrates (triglycerides) into adipose tissue, as well as stimulating the pathway of esterification of the fatty acids of triglycerides to glycerol 3-phosphate. This process leads to a very energy-efficient pathway for storage of dietary triglycerides in the postprandial phase.[27] Assuming that hyperinsulinaemia plays a major role in the development of human obesity, its reversal should have therapeutic potential.

The regulation of insulin secretion by the pancreatic β cell is extremely complex, and several neural, endocrine and paracrine factors interact to control this process.[28] The ventromedial hypothalamus (VMH) coordinates energy balance through both sympathetic and parasympathetic inputs to the β cell. The VMH integrates signals reflecting energy stores and recent nutritional state from the peripheral hormones insulin, leptin and ghrelin, and translates this information into signals for feeding through neurons releasing neuropeptide Y (NPY) and agouti-related peptide (AgRP), and into signals for satiety through neurons releasing α-melanocyte stimulating hormone and cocaine-amphetamine regulated transcript.[28] Experiments in animals and in humans have led to the hypothesis that the VMH damage increases vagal tone and autonomic activity, which leads to insulin hypersecretion by β cell, which results in the development of obesity.[29] This hypothesis of autonomic imbalance being a cause of obesity was first formulated in children and adults with hypothalamic obesity by Inoue and Bray[30] in 1979. Subsequently, autonomic imbalance proved to be a consistent feature of most known forms of massive obesity.[31] Based on their own experiments in animals with VMH lesions, King and Frohman[32] suggested that vagally mediated hyperinsulinaemia may explain up to 40% of the observed increase in fat content.

Somatostatin is a potent inhibitor of GH release and of several other peptides, including glucagon and insulin.[33] As described previously, inhibition of glucagon secretion by somatostatin is mediated via the SST_2 receptor, whereas the SST_5 receptor mediates somatostatin inhibition of pancreatic insulin secretion and contributes to the regulation of glucose homeostasis and insulin sensitivity.[7,16] Insulin release is controlled by a voltage-dependent outward K^+ current, which assists in closing voltage-dependent calcium-channels.[17] The somatostatin receptor is coupled to the voltage-gated calcium channel and somatostatin exerts its inhibitory action on channel opening.[34] In the presence of somatostatin, the magnitude of the calcium influx is attenuated, limiting the amplitude of the early insulin res-

ponse to glucose. The effect of somatostatin administration in humans on insulin and glucose kinetics was studied in acute experiments after an oral glucose tolerance test (OGTT) in obese and control subjects.[35] In both groups, somatostatin induced a delay in plasma glucose peak and an increase of plasma glucose levels during the late phase of the OGTT, whereas in terms of insulin levels, the authors observed a dose-dependent reduction in insulin secretion and a reduction of insulin/glucose ratio.[35] The results of this study and a similar one using a mixed meal[36] revealed a hyperglycaemic effect after acute administration of somastostatin, due to suppression of insulin secretion. However, this effect is rapidly reversed within a few days.[20] In contrast, the suppression of insulin response to glucose, chronically sustained, may limit adipogenesis and decrease obesity.

The influence of somatostatin analogues on carbohydrate metabolism was studied in patients with acromegaly, a disease characterized by a high incidence of glucose intolerance and diabetes mellitus. However, conflicting results have been reported in patients with acromegaly, and this is due to the divergent effects of somatostatin on glucose metabolism.[37-39] In fact, treatment with somatostatin analogues may reduce insulin resistance and glyconeogenesis by suppressing GH levels, but it also may decrease insulin and glucagon secretion.[40] The net drug-induced glycaemic effect is probably a slight but significant deterioration of glucose tolerance or diabetes, but the final result may vary depending on the metabolic background of each patient.[39] In any case, glucose monitoring is mandatory in acromegalic patients and in others receiving somatostatin analogues.

The action of somatostatin on the gastrointestinal tract may play a role in the generation of orexigenic or satiety signals to the CNS and, consequently, in the effectiveness of the drug on obesity treatment. Somatostatin and its analogues act predominantly in the small intestine, where they slow down small bowel transit. This effect is accompanied by inhibition of gastroenteropancreatic hormones such as insulin, glucagon, glucose-dependent insulinotropic polypeptide, glucagon-like peptide 1 (GLP_1), cholecystokinin, secretin, gastrin, neurotensin, pancreatic polypeptide.[28,41,42] Somatostatin also inhibits secretion of the orexigenic hormone, ghrelin.[43] Hence, somatostatin may inhibit several factors involved in the interplay between food intake and satiation. Moreover, drug-induced impairment of gallbladder and sphincter of Oddi motility, inhibition of bile secretion and altered biliary acid composition can increase the risk of gallstones, the incidence of which is already high in obese subjects.[42]

The issue of the drug effect on postprandial satiation was recently addressed in two double-blind, placebo-controlled studies.[44,45] In both studies, which were performed in healthy and obese subjects, administration of the somatostatin analogue octreotide significantly reduced postprandial sensations of hunger after a satiating meal. These results suggest an antisatiety effect and a permissive action of the drug in the development of obesity; however, they require further confirmation. In contrast, other actions of the drug with anorexigenic impact have been described, including slowing of gastric emptying and gastrointestinal motility with nutrient malabsorption, direct anorexigenic effects and direct effects on adipocytes.[20,46-48] Based on the available data, it is difficult to reach final conclusions on the role of somatostatin analogues on hunger and satiety. Insulin suppression seems to be the main mechanism responsible for weight loss in subjects receiving octreotide. A plausible explanation for this originates from experience in the use of the drug in acromegaly. If mechanisms other than insulin suppression were responsible for weight loss, patients with acromegaly receiving octreotide would be expected to lose weight and fat mass, which is not the case.[20]

The effects of somatostatin and its analogues on energy homeostasis are illustrated in figure 1.

2. Use of Somatostatin Analogues in Paediatric Hypothalamic Obesity

Hypothalamic obesity is a sequel to hypothalamic damage from tumour, surgery and/or irradiation resulting in intractable weight gain resistant to con-

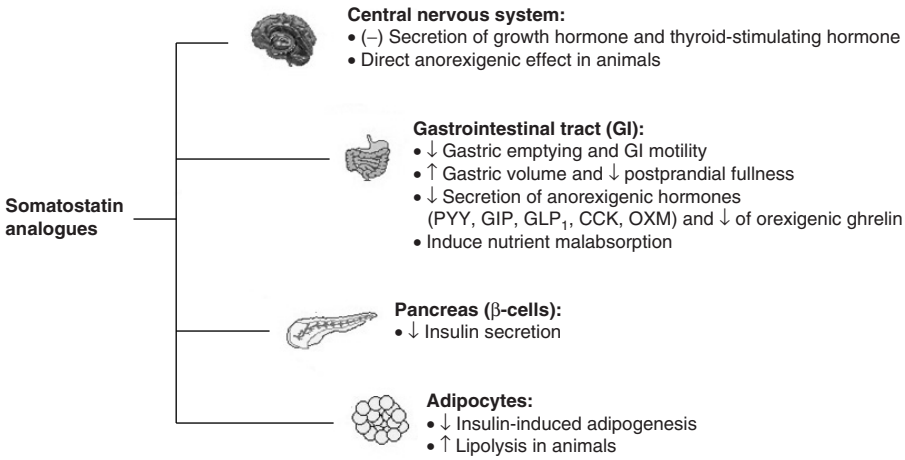

Fig. 1. The effects of somatostatin analogues on energy homeostasis. **CCK** = cholecystokinin; **GIP** = glucose-dependent insulinotropic polypeptide; **GLP_1** = glucagon-like peptide 1; **OXM** = oxyntomodulin; **PYY** = peptide YY; (–) indicates inhibits; ↑ indicates increases; ↓ indicates decreases.

ventional therapeutic measures.[49] The most common lesions that cause hypothalamic damage are craniopharyngiomas, other tumours, aneurysms, inflammatory and infiltrative diseases, and trauma. As a result of either the underlying disease or its treatment (surgery or radiotherapy), affected individuals gain weight and sometimes become markedly obese.[29] In children and adolescents, craniopharyngiomas are the most common cause of acquired hypothalamic damage. Craniopharyngiomas are rare, benign embryonic tumours that arise from ectoblast remnants of the Rathke pouch, located in the sellar/parasellar region.[50] The incidence is 0.2–2 new cases/million/year, 30–50% affecting children and adolescents.[51] The peak incidence is at 5–10 years of age, but the disease can occur in individuals of any age. Although the tumour is benign and the overall survival rate is high, there is considerable morbidity and impairment of quality of life (QOL). Obesity, often massive, is reported in 26–61% of these patients.[50] Children with craniopharyngioma already present with an increased body mass index (BMI) for age by the time of diagnosis, suggesting that the tumour itself impairs energy balance.[52] However, a rapid acceleration of weight gain is seen after surgery and/or irradiation, and obesity is present postoperatively in more than 50% of these patients.[52,53] The management of eating disorders and obesity in such patients is an extremely difficult task.

In addition to structural lesions, a number of genetic syndromes are associated with hypothalamic dysfunction and morbid obesity in children.[54] PWS and melanocortin-4 receptor mutations are considered to be the most common genetic forms of severe obesity in children.[55,56] Other genetic syndromes associated with severe obesity and hypothalamic dysfunction are leptin and leptin-receptor deficiency, and mutations of propiomelanocortin, prohormone convertase 1 and others.[29,54] These syndromes are extremely rare and are not discussed further in this article.

The pathophysiology of hypothalamic obesity involves both afferent and efferent neural signals of energy balance.[57] Briefly, the afferent arm of the circuit comprises the adipocyte hormone leptin, the β-cell hormone insulin and the gastrointestinal peptides ghrelin, peptide YY (PYY), GLP_1 and oxyntomodulin (OXM).[28,58] They all bind to their receptors within the VMH, providing information on nutritional status. Insulin and leptin provide signals from the periphery relating to long-term energy stores, and they decrease food intake. PYY, GLP_1 and OXM are released from the gut after a meal, and

they also stimulate anorectic pathways in the hypothalamus. In contrast, ghrelin, which is released from the stomach before meals, induces food intake.[58] The efferent arm of the circuit stimulates either the sympathetic or the parasympathetic nervous system. Sympathetic stimulation increases energy expenditure by activating β_3-adrenergic receptors, lipolysis and heat production, while parasympathetic stimulation, via the vagus, increases insulin secretion, adipogenesis and promotes energy storage. It is now recognized that weight gain in hypothalamic obesity results from both the inability of the damaged hypothalamus to transduce hormonal satiety signals from the periphery and the overactivation of the vagus nerve in the context of an autonomic dysfunction, which promotes insulin hypersecretion and weight gain.[29,57] Insulin hypersecretion appears to be a relevant abnormality in hypothalamic obesity and is probably a distinct phenomenon from the insulin resistance state that is found in common forms of childhood obesity.[59] Additional permissive factors for weight gain in these children are low levels of physical activity, increased somnolence, associated hormone deficiencies (such as GH, thyrotropin and gonadotrophin deficiency) and, overall, a low resting metabolic rate.[29]

Different therapeutic strategies have been attempted in hypothalamic obesity. However, successful treatment has been rarely achieved.[29] In the presence of hypothalamic damage, agents acting at other sites might offer some hope. Very recently, sibutramine, a reuptake inhibitor of both serotonin and noradrenaline (norepinephrine), was used in a double-blind, placebo-controlled study in children with hypothalamic obesity with partial success.[60] GH substitution therapy can decrease fat mass at least in patients in whom GH deficiency has been demonstrated.[61,62] The appreciation of the role of autonomic dysfunction and insulin hypersecretion in the pathogenesis of the syndrome led to some case reports of successful treatment with vagotomy,[63] which was not confirmed in subsequent trials.[64]

The group of Lustig et al.[65] in San Francisco attempted to use somatostatin analogues to inhibit insulin hypersecretion. In the first pilot study,[65] eight children with intractable, hypothalamic obesity (BMI 36 ± 2.5 kg/m^2) received octreotide for 6 months at a dosage of 5–15 μg/kg/day, in three divided doses. In comparison with a 6-month prestudy observation period, patients exhibited greater weight loss ($p = 0.04$) and BMI decrease ($p = 0.0001$) after treatment. The degree of weight loss correlated both with changes in insulin response on OGTT and changes in leptin levels. Calorie intake decreased by approximately 700 kcal/day and correlated with weight loss.[65] A second, double-blind, placebo-controlled, 6-month trial of octreotide in 18 subjects (age 13.8 ± 1.2 years, BMI 36.4 ± 2.4 kg/m^2) with hypothalamic obesity was performed by the same group.[18] Patients received octreotide subcutaneously (5–15 μg/kg/day) or placebo for 6 months. Octreotide was effective in stabilizing weight and BMI in the active-treatment group compared with placebo, but weight loss was less pronounced than in the previous study. Insulin secretion during the first 60 minutes of OGTT was clearly suppressed by octreotide. Finally, the children receiving octreotide demonstrated marked improvement in QOL, and this improvement correlated with the degree of insulin suppression.[18]

Safety issues relating to the use of octreotide were carefully analysed in this study.[18] All subjects receiving octreotide noted abdominal discomfort and diarrhoea, which resolved by the second month of therapy. Almost half of the patients receiving octreotide developed cholelithiasis or sludge formation at month 6. Treatment with ursodeoxycholic acid resolved the gallbladder abnormalities and patients remained free of this adverse effect until the end of the protocol. Finally, two subjects receiving octreotide developed mild glucose intolerance at 6 months, but none developed overt diabetes. The authors concluded from these two studies that insulin suppression therapy using octreotide may be a safe and effective therapeutic strategy in paediatric hypothalamic obesity with insulin hypersecretion. These preliminary positive results need to be confirmed by larger prospective studies and by other groups of investigators.

2.1 The Case of Prader-Willi Syndrome

PWS is one of the most common genetic causes of obesity, with a birth incidence of 1 in 29 000.[55] The syndrome is characterized by neonatal hypotonia, hypogonadism, growth deficiency, mental disability and characteristic facial features. This phenotype is thought to result from development abnormalities in the hypothalamus due to chromosome 15q11-q13 imprinted gene defects.[66] Individuals with PWS have increased appetite from childhood. Particular eating patterns comprise delayed meal termination, earlier meal initiation and return of hunger soon after a meal. Individuals with PWS eat longer and may consume on average up to three times more calories than controls.[67] The neurohormonal and metabolic basis for hyperphagia and obesity in PWS is still poorly understood. Postmortem neuroanatomical studies identified a reduction in hypothalamic anorexigenic oxytocin, but normal orexigenic NPY, AgRP, orexin and GH-releasing hormone neurons. Individuals with PWS have fasting and postprandial elevations in total plasma ghrelin.[68] The hyperghrelinaemia found in PWS led to the hypothesis that this disturbance could cause some of the features of PWS, which, in turn, could be ameliorated by lowering ghrelin levels. Octreotide has recently been shown to suppress ghrelin levels in animals and humans, and this inhibition appears to be mediated, at least in rats, via the SST_5 receptor.[69,70]

To investigate whether octreotide has therapeutic potential in PWS, a pilot study was conducted by Haqq et al.[71] In this study, administration of octreotide 5 μg/kg/day for 5–7 days decreased fasting ghrelin concentration in children with PWS, but did not fully abolish the normal meal-related suppression of ghrelin. In a double-blind, placebo-controlled trial, the effects of acute infusion of somatostatin on plasma ghrelin and appetite were examined in four young males with PWS.[72] Despite a significant lowering of fasting ghrelin levels by 60%, there was no associated reduction in food intake. In this study, somatostatin also significantly lowered plasma PYY levels and produced postprandial hyperglycaemia. The authors concluded that either hyperghrelinaemia does not contribute to hyperphagia in PWS or that concomitant reductions in anorexigenic gastrointestinal peptides by somatostatin counteracted any anorexigenic effects of lowering ghrelin.[72]

Another factor that could limit the benefit of somatostatin in PWS is the relative hypoinsulinaemia in these individuals, which is probably related to reduced visceral adiposity and decreased production of adiponectin.[73,74] The hypoinsulinaemia and the preserved insulin sensitivity could, at least in part, explain the hyperghrelinaemia in PWS.[75] The relative hypoinsulinaemia differentiates PWS pathophysiologically from other hypothalamic obesity syndromes, which are typically hyperinsulinaemic, and suggests that somatostatin analogues are unlikely to be an effective therapy of obesity in PWS. However, further prospective studies with a larger number of patients are needed.

Very recent studies with functional neuroimaging using positron emission tomography and functional magnetic resonance imaging are consistent with functional disorders in brain regions that drive eating behaviour and suppress food intake in patients with PWS.[76,77] Therefore, it appears more plausible that brain defects have a more important role than hormonal abnormalities in causing hyperphagia and obesity in PWS.[55]

3. Use of Somatostatin Analogues in Obese Adults

Encouraged by studies of childhood obesity, researchers further investigated the hypothesis that some hyperinsulinaemic obese adults might respond to the administration of octreotide.

In a pilot, uncontrolled study, long-acting release octreotide (octreotide LAR) 40 mg was administered in 44 severely obese adults (BMI 44.3 ± 1.0 kg/m^2) for 6 months.[78] The results showed that significant insulin suppression was achieved with octreotide LAR and this effect paralleled improvements in insulin sensitivity and BMI. When obese patients were grouped by BMI response into high responders (HRs: ΔBMI less than −3 kg/m^2), low responders (LRs: ΔBMI between 3 and

−0.5 kg/m^2) and non-responders (NRs: ΔBMI greater than −0.5 kg/m^2), HRs and LRs were found to exhibit higher suppression of excursions of insulin during stimulation tests than NRs. It is noteworthy that weight loss occurred without any dietary or exercise intervention. An additional finding of the study was the marked reduction of carbohydrate intake in the HR group and the decrease of carbohydrate-craving scores in both HR and LR groups. The authors attributed these changes to the reduction in hyperinsulinaemia, as only the subjects with the greatest insulin suppression decreased their daily consumption of carbohydrates.[78] In a separate analysis of this study, octreotide was found to reduce glucose-stimulated GLP_1 response, which further contributed to the insulin suppression.[79]

Recently, Lustig et al.[19] conducted a double-blind, placebo-controlled, multicentre trial to test octreotide LAR in obese hyperinsulinaemic adults for 6 months. The purpose of the study was to compare changes in weight at three different dose levels (20, 40 and 60 mg every 28 days) with placebo, and to identify the lowest dose of the drug that safely achieves optimal weight loss. It was shown that only patients receiving 40 or 60 mg of octreotide LAR experienced statistically significant weight loss, with mean differences from placebo in percentage weight change of 1.98% and 1.87%, respectively, and a BMI decrease, compared with baseline, of 0.73 and 0.79 kg/m^2, respectively. Patients with the highest degree of insulin hypersecretion appeared to benefit most from treatment. How-

Table I. Clinical studies in obesity using somatostatin analogues

Study (year)	Patients (n, diagnosis)	Treatment	Duration	Efficacy	Safety
Children					
Lustig et al.[65] (1999)	8 HO	Octreotide SC 5–15 μg/kg/d	6 mo	Decrease of BW, BMI and insulin (OGTT)	Transient digestive symptoms and gallbladder sludging in all patients
Lustig et al.[18] (2003)	9 HO 9 controls	Octreotide SC 5–15 μg/kg/d	6 mo	Stabilization of BW and BMI compared with placebo, suppression of insulin	9/9 transient digestive symptoms 4/9 gallbladder sludge or stones 2/9 IGT
Haqq et al.[71] (2003)	4 PWS	Octreotide SC 5–15 μg/kg/d	5–7 d	Decrease of fasting-plasma ghrelin. No change of BMI or insulin levels	3/4 mild diarrhoea
Adults					
Velasquez-Mieyer et al.[78,79] (2003/4)	44 morbidly obese	Octreotide LAR IM 40 mg/28 d	6 mo	Paralleled improvement of BMI, BF and insulin sensitivity. Suppression of GLP_1	Increase of HbA_{1c} within normal range
Lustig et al.[19] (2006)	172 hyperinsulinaemic obese	Octreotide LAR IM 20, 40, 60 mg every 28 d or placebo (multicentre, randomized)	6 mo	Significant decrease of BMI with the dosages of 40 and 60 mg/d every 28 d	Diarrhoea and cholelithiasis more common in octreotide LAR. Small significant increase of HbA_{1c} in all patients on active treatment. Increase of HbA_{1c} >7% (n = 5)
Gambineri et al.[81] (2005)	20 overweight or obese with PCOS	LCD and octreotide LAR IM 10 mg every 28 d (n = 10) or placebo (n = 10)	6 mo	Decrease of insulin levels. No change of BMI. Improvement of hyperandrogenism and restored ovulation	3/10 slight diarrhoea and abdominal pain

BF = body fat; **BMI** = body mass index; **BW** = bodyweight; **GLP_1** = glucagon-like peptide 1; **HbA_{1c}** = glycosylated haemoglobin; **HO** = hypothalamic obesity; **IGT** = impaired glucose tolerance; **IM** = intramuscularly; **LAR** = long-acting release; **LCD** = low-calorie diet; **OGTT** = oral glucose tolerance test; **PCOS** = polycystic ovary syndrome; **PWS** = Prader-Willi syndrome; **SC** = subcutaneously.

ever, there were no significant changes on QOL scores, body fat, leptin concentration, depression scores or macronutrient intake. Two adverse events, diarrhoea and cholelithiasis, appeared to be more common in groups treated with octreotide LAR than in the placebo group. The authors concluded that octreotide LAR given at 40 or 60 mg in hyperinsulinaemic obese patients resulted in significant weight loss and that the safety profile of the drug was similar to that in previous studies.[19]

The efficacy of octreotide and octreotide LAR was also tested in obese patients presenting with polycystic ovary syndrome (PCOS), a complex endocrine disorder characterized by hyperandrogenism and chronic oligo-ovulation. Some small trials showed that the drug can reduce hyperinsulinaemia and insulin resistance, improve hirsutism and even restore ovulatory menstrual cycles.[80,81] This last effect seems to be the consequence of the improvement in hyperinsulinaemia, as well as a direct effect of octreotide on the ovaries, as suggested by the recent discovery of somatostatin receptors at the ovarian level.[82] Therefore, the use of somatostatin in PCOS and other similar disorders with prominent insulin hypersecretion could be of interest, and somatostatin could be a potentially useful adjunct to metformin and thiazolidinediones.[82,83]

The most important clinical studies in obese children and adults using somatostatin analogues are summarized in table I.

4. Conclusion

Preliminary data show that somatostatin and its analogues, by limiting β-cell insulin secretion, are a potential target of obesity pharmacotherapy. Administration of somatostatin can retard weight gain in children with hypothalamic obesity and induce a small degree of weight loss in adults with hyperinsulinaemic obesity. More longer term and controlled studies by different groups are required to determine the precise indications of the drug, and to evaluate safety and cost-effectiveness issues in the treatment of obesity.

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