The clinical significance of somatostatin in pancreatic diseases

La signification clinique de la somatostatine dans les maladies du pancréas

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Abstract

The aim of the study was to provide knowledge on somatostatin and its action on the body, particularly the pancreas – in physiological and pathological conditions. In order to get to know the properties of somatostatin, a hormone discovered over forty years ago, many studies have defined its structure and the mechanisms by which it operates have been conducted. The properties of somatostatin receptors and the effect of somatostatin on the body – both a healthy one and in various disease stages – were determined. It was proven that the somatostatin had an inhibitive effect on the endo- and exocrine secretion of this organ, which allowed a hypothesis that it might play an important role in the pathophysiology of diabetes. In patients with severe acute pancreatitis, both somatostatin and octreotide appear to reduce the mortality rate significantly, without any effect on the incidence of complications. Nevertheless, somatostatin analogues may be the cause of acute pancreatitis. With regard to severe chronic pancreatitis, refractory to other forms of therapy, it was demonstrated that octreotide significantly alleviated pain in many patients. A similar risk of death, and generally a lower risk of complications were found in the group of somatostatin-treated patients with chronic pancreatitis when compared to those receiving placebo or untreated. The occurrence of hyperglycemia after the application of somatostatin analogues, and in particular after pasireotide, is disturbing. Somatostatin analogues have found application in the treatment of cancers. They may improve symptoms in patients with gastroenteropancreatic neuroendocrine tumors (NETs) and stabilize the tumor growth (PROMID study). However, the optimal hormone dose sizes and frequencies necessary to ensure a full therapeutic effect in selected diseases of the pancreas have not been completely determined.

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Keywords: Somatostatin; Acute pancreatitis; Chronic pancreatitis; Diabetes; Endocrine cancer

Résumé

L’objectif de cette étude est de fournir des connaissances sur la somatostatine et son action sur le corps, en particulier le pancréas, dans des conditions physiologiques comme pathologiques. De nombreuses études, qui définissent la structure et les mécanismes par lesquels la somatostatine exerce son activité, ont été menées sur cette hormone, découverte il y a plus de quarante ans. Les propriétés des récepteurs de la somatostatine de même que l’effet de cette hormone sur le corps – à la fois en bonne santé et à différents étapes de la maladie – ont été déterminées. Il a été prouvé que la somatostatine avait un effet inhibiteur sur la sécrétion endo- et exocrine du pancréas, permettant d’avancer l’hypothèse selon laquelle il pourrait jouer un rôle important dans la physiopathologie du diabète. Chez les patients atteints de pancréatite aiguë, la somatostatine aussi bien que l’octéotide semblent réduire le taux de mortalité de manière significative, sans aucun effet sur l’incidence des complications. Néanmoins, les analogues de la somatostatine peuvent être la cause de la pancréatite aiguë. En ce qui concerne la pancréatite chronique sévère, réfractaire à d’autres formes de thérapie, il a été démontré que l’octéotide atténuait de manière significative la douleur chez de nombreux patients. Un risque similaire de mortalité, et généralement un risque plus faible de complications, ont été retrouvés dans le groupe de patients atteints de pancréatite chronique et traités par somatostatine comparés à ceux recevant le placebo ou non traités. L’apparition d’une hyperglycémie après application d’analogues de la somatostatine, en particulier le pasireotide, est inquiétante. Les analogues de la somatostatine ont trouvé une application dans le traitement des cancers. Ils peuvent atténuer les symptômes chez les patients atteints de tumeurs neuroendocrines (TNE gastroentéropancréatiques) et stabiliser la croissance de la tumeur (étude PROMID). Cependant, les doses et fréquences optimales nécessaires pour assurer un plein effet thérapeutique dans certaines maladies du pancréas n’ont pas été complètement déterminées.

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Mots clés : Somatostatine ; Pancréatite aiguë ; Pancréatite chronique ; Diabète ; Cancer du système endocrinien

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1. Introduction

Somatostatin (SS) is a cyclic polypeptide, occurring in humans in two forms – one consisting of 14 amino acids and the other consisting of 28 amino acids [1]. It is a regulatory hormone produced by neurons, neuroendocrine, immune and inflammatory cells in response to neuropeptides, neurotransmitters, ions, nutrients, hormones, cytokines and growth factors [2].

Somatostatin-14 producing cells occur in most of peripheral organs [3]: liver, pancreas, lungs, immune system, urogenital tracts, kidneys and adrenals [4], whereas SS-28 is mainly produced by mucosal epithelial cells along the gastrointestinal tract [3]. This hormone affects many bodily functions – for example it inhibits pain, the release of hypothalamic hormones, it reduces the gastrointestinal activity and the T3/T4 release in thyroid. A relationship between the somatostatin and the secretory function of the pancreas has been demonstrated in many studies. Somatostatin decreases the expression of insulin, glucagon and PP genes. It causes a reduction in the secretion of endocrine pancreas and inhibits the release of bicarbonate and digestive enzymes from the exocrine pancreas [2,5].

The physiological effects of SS are achieved owing to the presence of transmembrane receptors [6] – the SSTR receptor family connected with the G-protein. In mammals, there are five SSTR subtypes: 1–5 [5]. The physiological actions of the somatostatin on the gastrointestinal tract, pancreas or immune system are mediated mainly by receptors 2 and 5 [7] – the expression of SSTR2 on the α cells and of SSTR 5 on the β cells has been demonstrated in numerous studies. It suggests that SSTR2 is responsible for the regulation of glucagon secretion while SSTR5 is involved in the regulation of insulin secretion [8]. Somatostatin-28 strongly inhibits the secretion of insulin from the pancreatic β cells [9]. Immunological studies have shown that the release of SS-28 from the stomach decreases the secretion of insulin after a meal, allowing thus the avoidance of undesirable hypoglycemia and the prevention of insulin sensitivity reduction in target tissues. Moreover, SS-14, secreted locally in δ cells, may also inhibit the β-cell function [10]. It has been demonstrated that SS-14 acts as a gastrin and glucagon secretion suppressor [11].

Somatostatin, and especially its synthetic analogue, octreotide, can modify the exocrine pancreatic secretion. The mechanism, by which somatostatin and octreotide affect this process, has not been fully investigated yet. Somatostatin may reduce the uptake of amino acids by the pancreas, as a consequence of a reduction of the enzymatic production and release [12]. Somatostatin release from pancreatic islets is stimulated by a high glucose concentration. This suggests that somatostatin acts in diabetes and other pancreatic diseases.

2. Acute pancreatitis

Autolysis of the pancreas, secondary to the activation of digestive enzymes, is the pathogenetic mechanism of acute pancreatitis (AP) [13]. On the basis of studies conducted on animals, it has been shown that the pancreatic exocrine function in acute pancreatitis is impaired and the course of improvement of its actions after severe insufficiency depends on the condition severity. Little is known about the exocrine pancreatic function in people with its acute inflammation, particularly during the acute phase. The only test available for humans shows a normal pancreatic digestive function in unstimulated patients suffering from mild to moderate acute pancreatitis in the early phase [14].

The first stage in the AP pathogenesis may be an abnormal activation of pancreatic proenzymes to their corresponding forms activated in the pancreas, i.e. a non-physiological position. In the pancreas, there are many defense systems to avoid the undesirable activation of enzymes. Such mechanisms include a strict division into enzymes and other cellular structures, especially lysosomes or physiological protease inhibitors (such as alpha-1 antitrypsin). However, if the protease-activating stimulus exceeds the capacity of these systems, an inflammation of the pancreas begins. The main idea underlying the specific treatment of this disease is to prevent the protease activity by means of antiprotease drugs [15]. Therefore, a possible treatment involves the enzyme secretion inhibition. Studies conducted on animals have shown a significant reduction of secretion in pancreatic inflammation, but studies conducted on humans are not conclusive [16]. If the level of antiprotease molecules in the pancreas increases, the risk of pancreatitis decreases and/or the risk of damage (necrosis) reduces. However, some authors suggest that if the secretion of pancreatic enzymes is inhibited, the number of proteases probably decreases and, consequently, a higher risk of pancreatic self-digestion is observed. Because somatostatin and somatostatin analogues are the strongest pancreatic exocrine secretion inhibitors, their use in the treatment of acute pancreatitis should be fully justified. These drugs may reduce or completely inhibit the response of pancreatic and gastrointestinal hormones after meal [15]. Despite experimental and clinical studies, the role of antiproteases and pancreatic secretion inhibitors (like somatostatin or its analogue – octreotide) remains unclear [13].

Since the SS discovery in 1970s, a number of its clinical uses have been proposed – it seemed that acute pancreatitis would be a disease responding to the somatostatin therapy [15].

The first clinical study by Limberg and Kommerell, in which somatostatin was used in acute pancreatitis, was published in 1980. In a study involving 14 patients, “impressive clinical improvement in all patients” were found. This promising discovery was tested in several controlled clinical trials. Although patients treated with somatostatin showed a lower incidence of complications, mortality, and improved biochemical parameters, it was not possible to determine the statistical significance [16]. Because of the short SS half-life, it was necessary to invent its synthetic analogues, including octreotide (OCT), with a longer biological activity and with a stronger action. The SS and OCT effects the on the course of acute pancreatitis were studied. Results indicated the usefulness of exocrine pancreas inhibiting drugs (especially SS) in the treatment and prevention of acute pancreatitis. Some authors also suggest a “cytoprotective” effect of somatostatin and octreotide, which can positively influence the outcome of the acute pancreatitis treatment [15]. Somatostatin and its long-acting analogue, OCT, are potent pancreatic exocrine secretion inhibitors. Studies were conducted on their
effect on mortality in experimental acute pancreatitis. Since a significant impact on the mortality rate showed only in the meta-analysis, the somatostatin therapy in AP has not become a standard practice. In multicentre studies, where OCT was used in moderate to severe acute pancreatitis, no significant benefits of this drug on the course of the disease have been shown [17].

Trials in patients with moderate to severe acute pancreatitis showed lower (although not statistically significant) rates of complications in patients treated with octreotide in doses of $3 \times 200$ and $3 \times 500 \mu g$/day, when compared to the control group and to patients receiving a lower dose of octreotide [16]. In patients with severe AP, both SS and octreotide seem to reduce the mortality rate significantly, with no effect on the incidence of complications. Data from eight studies in which SS was used and data from six studies in which OCT was used show that the mortality rate in the control and in treated cases was, respectively, 22.7 vs. 9.8% for SS, and 25.6 vs. 14.4% for OCT. Although the reason underlying the use of SS and octreotide in acute pancreatitis is for them to inhibit almost all pancreatic functions, other important properties of these measures should not be forgotten, for example a hemodynamic effect of a visceral blood flow reduction, the reticular liver stimulation and the cytokine cascade modulation. In the severe AP pathogenesis, all these characteristics, common to SS and OCT, may be more important than their inhibitory effect on pancreatic secretion [13].

Results of clinical trials in which SS and OCT were applied in the treatment of patients with AP have been used for the meta-analysis. Early and overall mortality, complications, and the percentage of patients who required surgical treatment were evaluated. Basing on these results, an initial proposal was hypothesized that antisecretory factors such as SS and OCT might reduce mortality without affecting the complications [13,15]. In addition, studies show that an early somatostatin treatment significantly reduces the incidence of pancreatic complications (pancreatitis, pain and amylase enzyme activity), while it seems that octreotide only reduces the higher amylase activity [15]. The studies evaluated the OCT effect on severe acute pancreatitis. Only patients with moderate to severe pancreatitis were included in the study. After randomization, eight patients in each group were administered octreotide subcutaneously in doses of $3 \times 100 \mu g$/day, $3 \times 200 \mu g$/day or $3 \times 500 \mu g$/day for 10 days [16]. In total, 24 patients (10 men, 14 women, average age 58 years) were treated with octreotide. One hundred and eight patients with acute pancreatitis were used as a control group. Three groups treated with octreotide and the control group were comparable in terms of age, sex and severity of pancreatitis. Two patients treated with OCT died because of septic complications, which are still the most important cause of death in acute pancreatitis in humans. In the groups treated with octreotide in doses of $3 \times 200$ and $3 \times 500 \mu g$/day, a lower rate of complications was observed than in the low-dose octreotide groups and in the control group. However, due to the small number of patients, the results do not have statistical value [16].

In contrast, studies conducted by Uhl et al. showed no benefits from the use of octreotide in the treatment of moderate to severe acute pancreatitis. It was a high quality test and should be reliable [18]. Moreover, based on the results of the previous year meta-analysis, it was found that there were no apparent benefits from the application of octreotide in primary moderate to severe acute pancreatitis with reference to the main treatment results [19].

The main problem in the acute pancreatitis treatment process, particularly the severe form of this disease, is the difficulty in conducting clinical trials which ensure a reliable and statistically significant response to the proposed action of various therapeutic agents. According to the AP pathophysiology, the efficacy of already available drugs, including somatostatin, should be re-evaluated and possibly they should be administered differently. To test this hypothesis, an adequate study should be conducted [20].

Acute pancreatitis is the most common complication of the endoscopic retrograde cholangiopancreatography (ERCP), occurring in 1–10% of patients. The risk of acute pancreatitis amounts to 1–2% after ERCP, 1–4% after the biliary endoscopic sphincterotomy (ES), 4–8% after the ES of the pancreas and 13–35% after the small ES of the pancreatic papilla. Although the course of the complications is usually mild, it usually requires a few days of hospitalization. A lot of substances were used to prevent such complications, mainly through the pancreatic secretion inhibition. The somatostatin effect was evaluated in several studies and their results were questionable. This hormone inhibits pancreatic exocrine secretion by reducing the release of secretin and cholecystokinin. Somatostatin also reduces the intrapancreatic pressure in the duct by inhibiting the sphincter of Oddi motility [21]. The presence of somatostatin receptors was found in the sphincter of Oddi in pigs, opossums and in humans. The impact of somatostatin on the sphincter is different in different species. Physiologically, the sphincter of Oddi motility is characterized by a basal activity regulated by cholinergic innervation (vagus nerve) and a low frequency of the phasic activity [15]. Somatostatin reduces the pain after ERCP but its impact in the prevention of pancreatitis has not been specified. It was shown that the use of SS resulted in a lower frequency of occurrence of pancreatitis, but no statistically significant results were obtained [21].

The study in which octreotide was used to prevent pancreatitis after ERCP of the pancreas failed to get results better than with placebo. This study suggests that octreotide may not protect against ERCP induced pancreatitis [22]. It was found that the excitatory effect of octreotide on the sphincter of Oddi (SO) might impair the biliary and pancreatic duct outflow. In another study by Manolakopoulos et al., it was found that octreotide increased the frequency of SO phasic contractions and, since the bile flow in humans is primarily passive, it could impair the flow of bile and pancreatic juice into the duodenum. It was hypothesized that octreotide might fail to prevent pancreatitis because it could induce the sphincter of Oddi dysfunction [23]. The effect of octreotide on the sphincter of Oddi is still controversial: some experimental studies on dogs showed a reduction in the SO motility after octreotide [24], while other studies demonstrated that the octreotide induced the SO excitation in response to drug administration by infusion [25]. Another study conducted by Cavallini, showed abnormalities in the pancreas outflow after the administration of octreotide to healthy volunteers.
In another study on patients with idiopathic recurrent pancreatitis, it was demonstrated that acute administration of octreotide might induce tachyphylaxis and, consequently, a rise in the sphincter of Oddi pressure, with possible impairment of the biliary-pancreatic outflow. This effect may impair pancreatic juice drainage, trigger pancreatitis or worsen it in case of patients with pancreatitis [27]. After the octreotide administration to a patient with acute pancreatitis, the disease worsened, while, when administration was discontinued, the patient’s condition improved. It was observed that octreotide might cause acute pancreatitis by inducing the sphincter of Oddi spasm [28]. A similar situation occurred in a few patients with acute pancreatitis also treated with octreotide [29]. Caution is required during the octreotide therapy in case of patients with acute pancreatitis, and the provision of information about the side effect of octreotide should be part of this drug administration.

3. Chronic pancreatitis

Chronic pancreatitis (CP) is a painful disease manifested by the pancreas failure [30] and by an increase in the number of SS and PP producing cells in the pancreas [31]. The disease occurs with a frequency of 27.4 per 100,000 people. The main cause (70–90%) of chronic pancreatitis in Western countries is the consumption of alcohol. The second most common form of chronic pancreatitis (25%) is idiopathic pancreatitis in patients without identified risk factors. This group steadily decreased along with the growing awareness of genetic risk factors [14]. Studies have shown that cigarette smoking may play an important role in the development of endocrine disorders in the progress of chronic pancreatitis. Smoking patients with CP showed a higher number of SS and PP secreting cells and their different spatial distribution in relation to non-smoking patients and to healthy individuals. SS producing cells in the pancreas of healthy people are located mainly on the outskirts of islets. In patients with chronic pancreatitis, δ cells are located throughout the area of the islets and between the follicular cells in the exocrine pancreas. In healthy people, PP secreting cells can be found in the islets in the pancreatic head and tail. In non-smoking patients with chronic pancreatitis, PP cells can also be found in the pancreatic body and between the follicular cells. In smoking patients with CP, PP cells are located in the islets of the entire length of the pancreas (head, body, tail), and between the follicular cells. In the pancreas of CP smokers, the observed amount of PP cells was 3 times bigger than in healthy subjects and approximately 2 times greater than in CP patients who did not smoke. The highest number of PP cells was observed in the pancreatic head, whereas in case of healthy people and non-smoking patients with CP, the highest amount was found in the tail. In case of smokers, the amount of α and β cells decreased. In addition, patients who smoke cigarettes have a 20% increased risk of pancreatic calcification when compared to those who do not smoke [31].

The predominant symptom of chronic pancreatitis is a sharp, dull epigastric pain radiating to the back, which can be partially relieved by bending forward. The pain is often associated with nausea and vomiting. Tenderness in the upper abdomen is common. Patients often avoid eating because of the pain. This leads to a significant weight loss, particularly if the patient has steatorrhea. One third of the patients develop overt diabetes mellitus, which is usually mild [32]. Chronic pancreatitis is considered to be a process associated with overexpression of fibroblasts and growth factors, increased expression of interleukin-8 and disturbances in the homeostasis of cholecystokinin. These different factors in combination can eventually lead to irreversible organ damage. Octreotide has been studied in the treatment of chronic pancreatitis. As a somatostatin analogue, the drug inhibits the pancreas secretion and significantly reduces the levels of CCK. Initially, there were many small, short-term studies considering the use of this drug, but they did not produce conclusive results. A multicenter pilot study was made in 1993 to explore different dosing regimens – it showed that 200 μg of octreotide given subcutaneously three times a day was more effective than placebo. Octreotide significantly relieved the pain in many patients with severe chronic pancreatitis, which was resistant to other forms of therapy [33].

Pain is a major clinical manifestation of chronic pancreatitis. Effect on pain in the inhibition of pancreatic secretion by octreotide was tested in two studies. The first study showed no significant reduction in pain after a three daylong treatment with octreotide. The second study, in which octreotide was used for three weeks, showed a significant reduction in pain when compared to placebo. The most common complication of chronic pancreatitis is the formation of pseudocysts – there is evidence that octreotide may be useful in their treatment [16].

In the study in which seven patients with CP who had developed pancreatic pseudocyst were treated – octreotide was used in a dose of 3 × 100 μg/day for two weeks. Four of seven patients responded to the treatment immediately, and the average size of pseudocysts decreased by 42%. In addition, pain relief was observed. Other studies were carried out on infected pancreatic pseudocysts. After a week of treatment with a dose of 300 μg/day of octreotide, the cyst was reduced from 8 cm to 1 cm and the secretion drainage decreased from 200 mL/day to 30 mL/day. It is suggested that the damaged pancreas responds to somatostatin to a lesser extent. However, the positive results of the treatment with octreotide in patients with chronic pancreatitis indicate that secretion of inhibitory substances can be a new concept of treating these patients [16].

4. Diabetes mellitus

The most common disorder of the endocrine pancreas is diabetes. Beta cells damaged by inflammation secrete less insulin [34]. The pathophysiological mechanisms leading to exocrinepancreatic insufficiency in diabetes are not fully understood. They appear to involve an imbalance between pancreatic islet hormones – stimulatory (insulin) and inhibitory (glucagon, somatostatin), angio-path-caused fibrosis of the pancreas, autoimmune mechanisms, autonomic neuropathy and modified release of nutrient regulatory mediators [14]. Immunohistochemical studies showed an increase in the number somatostatin-secreting cells in patients with diabetes when compared to people without diabetes [35]. The change the number of cells that secrete somatostatin can be caused by a deficiency
of insulin, although the insulin therapy did not result in a reduction of the concentration of somatostatin in δ pancreatic cells in patients with diabetes. On the other hand, it was found that the absolute and/or relative excess of glucagon could also lead to a compensatory increase in the quantity of somatostatin [5,36].

4.1. Diabetes type 1

In patients with type 1 diabetes (insulin-dependent), there was an increased number of δ cells and the ratio of cells δ to α decreased due to an excessive proliferation of α cells. Increased basal level of SS in plasma and increased pancreatic δ-cell response to arginine were observed, while the total postprandial concentration of SS was reduced. Insulin treatment normalizes the elevated plasma concentrations of SS in these patients. The cause of elevated levels of SS in type 1 diabetes is unclear—many factors may be involved in this phenomenon (including the chronic exposure of δ cells to hyperglycemia, ketones, hyperglucagonemia or lack of circulating insulin). It is possible that that chronic overproduction of SS in type 1 diabetes prevents the body from extreme hyperglucagonemia. On the other hand, the increase in SS secretion may worsen the severity of type 1 diabetes. The abnormal SS secretion in response to food intake may explain the excessive secretion of glucagon in patients with type 1 diabetes [37]. In type 1 diabetes, the concentration of somatostatin secreted in the upper part of the intestine (which is the major source of circulating somatostatin) is increased. It is generally believed that somatostatin plays only a minor role in inhibiting the activity of pancreatic α cells in healthy humans and animals. This suggests the influence of locally released somatostatin on the stimulated, but not on the basic secretion of insulin. Because most of β cells are destroyed in diabetes, somatostatin becomes a major paracrine inhibitor of α cells [36].

4.2. Diabetes type 2

In patients with type 2 diabetes, the number of α cells and δ cells is increased, and the ratio of δ cells to α cells decreases. The increase in SS concentration in response to meal or exogenous glucose is significantly reduced and an insulin treatment may restore the SS response to hyperglycemia. In patients with type 2 diabetes with normal levels of insulin, normal SS secretion, stimulated by fatty meal, is observed, which suggests that physiological concentration of insulin is essential to achieving a corresponding increase in the SS secretion. Both in patients with type 1 and type 2 diabetes, δ cell growth, decreased δ/α cell ratio and impaired glucose-stimulated SS secretion have been demonstrated. The basal physiological level of SS in type 1 diabetes is increased, while in type 2 it is at a normal level [37].

Recent data suggest that somatostatin-28 acts in healthy humans as a nutrient-stimulated insulin secretion inhibitor—it acts as a hormone that inhibits the activity of the endocrine pancreas. Somatostatin-14 acts as a suppressor of glucagon and gastrin secretion. Both forms of SS may also act as neurotransmitters. In most studies, the SS plasma levels are measured as somatostatin-like immunoreactivity (SLI). Immunoreactivity is measured by using the antibodies recognizing an epitope in pro-somatostatin. It has been observed that patients with type 1 diabetes have an increase in SLI, which is corrected by the normalization of glucose levels in blood. Patients with type 2 diabetes have a higher or similar basic SLI levels compared to the control group. Based on predictions stating that SS-28 acts as a physiological inhibitor of β cells, it was postulated that its increased levels might contribute to the abnormal function of these cells in diabetes. Due to the availability of methods to separate analyzes of SS-14 and SS-28, it was estimated that there is a possibility that the concentration of these two peptides altered in patients suffering from type 2 diabetes after a fatty meal. The study included nineteen men—patients with diabetes and healthy subjects (control group). The SS concentration is significantly increased in the plasma of patients with diabetes, and also in the plasma of healthy subjects. There was no difference between the basal SS concentration in sick patients and in healthy people of the control group. There was also no difference in the concentrations of SS after a fatty meal [11]. There were no differences in the overall response of SS-28 to a fatty meal between these two groups [11].

There are ongoing trials concerning the application of somatostatin as an endogenous peptide with a neuroprotective action in the prevention of diabetes-induced retina neurodegeneration. The study was conducted on rats with streptozotocin-induced diabetes. Animals were treated with somatostatin in the form of eye drops for 15 days. It was observed that somatostatin therapy prevented disturbances in the electroretinography and the neurodegeneration evaluated by measuring the glial activation and apoptosis in diabetic rats [38]. Clinical studies are needed in order to determine the exact application of somatostatin in the treatment retinal neurodegeneration induced by diabetes [39]. In a study by Corbould and Campbell, it was found that the use of octreotide for the treatment of severe diarrhea in a patient with type 1 diabetes is effective and well tolerated [40]. Nevertheless, there are a number of studies showing that the use of somatostatin analogues has many adverse effects [41–43]. The most common side effects are symptoms of the gastrointestinal tract and vascular disorders. Most of them are resolved spontaneously without a dose adjustment or temporary discontinuation. Mild transient elevations in liver enzymes are reported in 29% of patients, and are in most cases resolved spontaneously without treatment discontinuation [41]. However, what is disturbing is the presence of hyperglycemia after the application of somatostatin analogues, and in particular after the application of pasireotide [41–43]. In a study by Colao et al., hyperglycemia was observed in 73% of patients and 6% of patients discontinued the study because of this event. Glucose levels and glycosylated hemoglobin increased soon after the pasireotide treatment started. There is an increased risk of hyperglycemia, as an adverse effect, in case of patients with pre-existing diabetes or impaired glucose tolerance [41].

Results of studies on healthy volunteers suggest that hyperglycemia caused by pasireotide is the result of decreased insulin and incretin secretion. Hepatic and peripheral insulin sensitivity remains unchanged [44]. Many studies have demonstrated the SSTR2 expression of cell-α and SSTR5 expression of cells-β,
which suggests that in physiologic conditions somatostatin regulates the glucagon and insulin secretion [8,45]. Somatostatin analogues: octreotide and lanreotide, have affinity for receptor subtype SSTR-2 and, therefore, have less impact on the secretion of hormones than pasireotide, which inhibits the secretion of insulin much more heavily than glucagon because of its high affinity for SSTR-5. Probably the dependence between the number of receptor SSTR-5 and receptor SSTR-2 substantially affects the occurrence of hyperglycemia after the pasireotide treatment [42,46]. In studies on patients with type 2 diabetes, in which octreotide was used, no effect on hyperglycemia was observed. It was found that this analogue was not sufficiently selective to be therapeutically useful in non-insulin dependent diabetes [47]. Octreotide was used in patients with glucagonoma and diabetes [48].

5. Pancreatic adenocarcinoma

A large number of different primary tumors and their metastases have a significant amount of SSTR somatostatin receptors. The SSTR mRNA analysis shows that human tumors of neuroendocrine origin and tumors derived from the gastrointestinal tract, glioma, meningioma, prostate, lung and breast cancer cells express multiple SSTR receptor subtypes, the most common one being SSTR2. Most of these tumors also express SSTR5 and, to a lesser extent, SSTR1, SSTR3 and SSTR4 [49]. Somatostatin and its analogues can indirectly control the tumor growth and metastasis by angiogenesis inhibition (tumor angiogenesis is essential for growth, tumor invasion and metastasis). The overexpression of peritumoral vascular somatostatin receptors with high affinity for somatostatin and octreotide was described for human primary colorectal cancers, small cell lung cancer, breast cancer, kidney cancer and malignant lymphoma [50]. The ability of somatostatin to inhibit the growth of normal and some tumor cell lines and the ability to reduce the growth of experimentally induced tumors in animal models has led to attempts to use the somatostatin analogues in the treatment of tumors [7]. The effect of inhibiting tumor growth by somatostatin can occur by way of at least two mechanisms (depending on the receptor). One is the inhibition of the mitogenic signaling of the growth factor receptor kinase, thereby inhibiting the growth by stopping cell cycle. The second mechanism, which was confirmed by flow cytometry and morphological studies, is the induction of apoptotic cell death [51]. The effect of tumor growth inhibition by somatostatin can occur via direct and combined action on tumor cells by inhibiting the expression of the growth factor receptor, MAPK inhibition and PTP stimulation [7]. Somatostatin activates the tyrosine phosphatases in the human pituitary adenomas, in the colon cancer cells and in the skin cancer cells. SS also activates a serine/threonine phosphatases. The activation of pP2B protein phosphatase caused by SS is observed in rat sympathetic neurons, in the α and β cells in mice. SS negatively regulates the MAP kinase activity in different cell lines – in human endothelial cells, tumor cells, lung cancer cells, breast, pituitary adenomas. In contrast, in human skin cancer cells, SS activates MAPK [52]. The binding of somatostatin to SSTR2 seems to lead to stop the cell cycle in the G0-G1 phase and then to apoptosis. The SSTR2 expression in human pancreatic cancer results in a significant slowdown of the cell division by a mechanism independent of somatostatin [51]. Somatostatin may have indirect effects on the tumor growth by inhibiting the circulating, paracrine and autocrine factors which initiate tumor growth. It may also modulate the activity of immune cells and affect the blood supply to the tumor, partly inhibiting the angiogenesis [7].

The endocrine pancreatic insufficiency may result in tissue damage, due to the obstruction of the pancreatic duct in consequence of a tumor/pancreas surgery, which leads to a minimization or complete loss of the organ. The majority of patients with pancreatic tumors have pain and weight loss as the dominant symptoms [14]. Somatostatin inhibits not only the activity of the exocrine and the endocrine pancreas, but also the in vitro tumor DNA synthesis [53].

In the course of pancreatic cancer, there are also disorders of the carbohydrate metabolism – diabetes may be the first symptom of pancreatic adenocarcinoma [34].

Studies have shown that using somatostatin may be an effective adjuvant therapy for receptor-positive adenocarcinoma of the pancreas. Somatostatin and its analogues cause a reduction in the tumor size and prolong the survival in the animal pancreatic cancer models. Expression of somatostatin receptor appears to be a prerequisite for inhibiting the growth of pancreatic cancer by SS and its analogues [51]. When somatostatin receptors are located in pancreatic tumor cells, somatostatin analogues inhibit their proliferation both in vivo and in vitro. An increase in the concentration of functional somatostatin receptors on pancreatic adenocarcinoma cells can make pancreatic cancer cells more sensitive to growth inhibition by somatostatin or its analogues [53].

Somatostatin and its analogues were used in the treatment of pancreatic cancer in clinical trials because of their inhibitory effect on a variety of biological processes, including cell proliferation. The SSTR2 gene was the most successful and the most frequently used in gene therapy. SSTR1 and SSTR5 also showed inhibitory effects on the growth of pancreatic cancer, while the SSTR3 and SSTR4 genes showed no significant inhibition [54].

Somatostatin has the ability to inhibit tumor growth and metastasis by an activation of the SSTR receptors located on both cancer cells and, for example, tumor vascular endothelial cells responsible for tumor neovascularization. The anti-angiogenic properties of SS are mediated by an activation of SSTR2 and SSTR3, which results in blocking the proliferation and the migration of endothelial cells and in the monocyte activation lock. It also causes inhibition of the release of pro-angiogenic factors such as vascular endothelial growth factor (VEGF), PDGF, IGF-1 and basic fibroblast growth factor (bFGF) [55].

6. Pancreatic endocrine tumors

6.1. Pancreatic endocrine tumors

Pancreatic endocrine tumors, also called pancreatic endocrine tumors (PET), constitute 2–10% of all cancers of the pancreas. The most common endocrine tumors include insulinoma (about 17%) and gastrinoma (about 15%). Less
frequent are VIP-oma, glucagonoma, somatostatinoma and carcinoid tumors that secrete serotonin [34].

Insulinoma are the most common pancreatic islet cell tumors. The accompanying symptoms may include hypoglycemia due to an excessive production and secretion of insulin. Insulinoma are mild in 90% of cases and in 99% of cases they are located in the pancreas. Studies suggest that insulinoma express SSTR1 and SSTR2, while expression of SSTR5 by the tumor shows a positive correlation with the size of tumor and its virulence [37]. Somatostatin and its analogues are used to inhibit the excessive secretion of insulin that occurs in the course of insulinoma. The SS action results in a remission of hyperinsulinemia and the associated hypoglycemia. Somatostatin is used to treat hyperinsulinemia associated with hypothalamic obesity, and also for the treatment of primary hypersecretion of insulin [10].

Glucagonomas—glucagon-secreting tumors, represent the third most common type of islet cell tumors. Also, 70% of these tumors are malignant. Glucagonoma show a high expression of SSTR2 and less expression of SSTR5, which is also characteristic for normal alpha cells [37]. Gastrinoma (gastrin-producing tumors) represent up to 20% of the pancreatic endocrine tumors. They can cause stomach ulcers due to the increased gastric acid secretion. In gastrinoma, the SSTR2 expression (up to 100%) and SSTR5 (76–100%) is observed predominantly—it correlates well with the octreotide treatment [37].

VIPomas are tumors producing the vasoactive intestinal peptide; they are often located in the islets. The SSTR5 expression appears to be primarily present in somatostatinoma, and SSTR2—predominantly in VIPomas [37]. Somatostatinoma (somatostatin-producing tumors) show malignancy in 90% of cases. Along with the PP-producing tumors, they are extremely rare [37]. Somatostatinoma are rare neuroendocrine tumors that usually arise from transformed δ cells in pancreas or in duodenum, but sometimes also in other places, including the papilla of Vater. Clinical syndromes of excessive secretion of somatostatin are fatty stools, cholelithiasis, hyperglycemia and weight loss, along with non-specific symptoms of the presence of a tumor in the abdomen. Polymorphisms in the somatostatin, SSTR2 and SSTR5 genes were identified, but no clear relationship between alleles and disease states has been observed so far. Individual reports have described somatic mutations in SSTR genes, which may be pathogenetically important in somatotroph pituitary adenomas and human pancreatic cancer cells [7].

Neuroendocrine tumours (NETs) are a genetically diverse group of malignancies that sometimes produce peptides causing characteristic hormonal syndromes. They may release neurohormones and biogenic amines (up to 8% of cases), which may decide about the clinical symptoms [56]. NET tumors are more common than it was previously suspected. Neuroendocrine tumors express a high density of SSTR—it was determined by reverse polymerase chain reaction (RT-PCR) and immunohistochemistry. Many neuroendocrine tumors express somatostatin receptors, which makes them excellent potential therapeutic targets. Numerous studies have shown that the administration of somatostatin analogues is associated with the disease stabilization and a long-term survival [57,58]. The native somatostatin form is not useful in clinical practice due to its short half-life (<2 min), therefore its analogues are used. They constitute the first line of medical therapy for a well-differentiated NET [59,60]. Octreotide binds with high affinity to SSTR2 and 5, and inhibits the secretion of peptides and amines from the neuroendocrine cells [61]. Lanreotide is another analogue used in the treatment of NET. It has a similar binding profile as octreotide. Pasireotide, an analogue of somatostatin, which has high affinity for four out of five somatostatin receptor subtypes (SSTR1-3 and SSTR5) [42,58,60], exhibits a 40-fold higher affinity, and 158-fold higher functional activity at the receptor SSTR5 than octreotide. The mechanism by which the somatostatin analogues normalize bowel function it is still unclear. However, it was found that the use of analogs causes the following: inhibition of intestinal hormones, prolonged time of intestinal passage, increased absorption of water and electrolytes, and reduced visceral blood flow [58].

6.2. Carcinoid tumors

The octreotide treatment may also improve the survival of patients with carcinoid tumors [62]. Recently, it has been hypothesized (PROMID study: double-blind, placebo-controlled and randomized phase IIIb studies) that octreotide LAR prolongs time to tumor progression and survival. Patients were randomized to placebo or octreotide LAR 30 mg intramuscularly at monthly intervals to tumor progression or death. The primary efficacy endpoint was time to tumor progression. The median time to tumor progression in the octreotide LAR group and placebo was 14.3 and 6 months, respectively (hazard ratio [HR] 0.34, 95% CI, 0.20 to 0.59, P = 0.000072). It was observed that octreotide LAR significantly prolonged time to tumor progression as compared to placebo in patients with a functionally active and inactive metastatic midgut NET. Furthermore, the PROMID study has shown that the benefits of treatment with octreotide in NET are independent of the level of CgA, Karnofsky performance status and age of the patient [63]. The Cancer Network has updated its guidelines based on the PROMID data, to include octreotide LAR as a management option for asymptomatic patients with recurrent, unresectable metastatic NETs [58]. Unfortunately, patients with NET treated with SSTR2 analogues—preferring such as octreotide and lanreotide—may experience loss of response, 6–18 months after initiation of treatment [64]. The exact mechanism of this phenomenon is still unknown. This has led researchers to become interested in a somatostatin analogue, which can be equally effective and well tolerated by patients. Pasireotide may satisfy this role in the future due to its high affinity to the SSTR1-3 and SSTR5 receptors. Pasireotide 600–900 administered subcutaneously was effective and generally well tolerated in controlling the symptoms of carcinoid syndrome in 27% of patients with advanced NET refractory or resistant to treatment with octreotide LAR [65]. Furthermore, there are studies on a novel compound that binds to receptors SSTR2 and D2 [58].
7. Summary

In patients with severe acute inflammation of the pancreas, the administration of somatostatin significantly reduces mortality, no effect on the incidence of complications. It was found that there is no apparent benefit in the application of octreotide in primary moderate to severe acute pancreatitis in relation to the main results of treatment. Caution is required during the octreotide therapy in case of patients with acute pancreatitis, and the provision of information about the side effect of octreotide should be part of this drug administration.

In patients with chronic pancreatitis somatostatin-treated group compared to those receiving placebo had similar risk of death, and generally lower risk of complications. The other hand octreotide substantially alleviates pain in many patients with severe chronic pancreatitis, which is resistant to other forms of therapy.

Both in patients with type 1 diabetes and type 2, the number of cells α and δ is increased, and the ratio of δ to α cells decreases. In diabetes 1 and 2, demonstrated impaired glucose stimulated secretion somatostatin. Basic physiological somatostatin concentration in type 1 diabetes is increased, while in type 2 diabetes is at a normal level. Use of somatostatin analogues, especially pasireotide is the reason of hyperglycaemia. In human tumors of neuroendocrine origin shown to express multiple SSTR receptor subtypes, the most common SSTR2. Somatostatin and its analogs may indirectly control the tumor growth and metastasis by inhibition of angiogenesis by inhibiting the cell cycle, or induce apoptotic cell death. Recently, it has been hypothesized (study PROMID) that octreotide LAR prolongs time to tumor progression and survival.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References


