Disponible en ligne sur
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com

Annales d'Endocrinologie 75 (2014) 232–240

Annales d'Endocrinologie
Annals of Endocrinology

Review

The clinical significance of somatostatin in pancreatic diseases

La signification clinique de la somatostatine dans les maladies du pancréas

Mariola Śliwińska-Mossoń *, Marta Veselý , Halina Milnerowicz

Department of biomedical and environmental analysis, Wrocław Medical University, 211 Borowska, Poland

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 that define 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.

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 stades 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 pathophysiologie du diabète. Chez les patients atteints de pancréatite aiguë sévère, la somatostatine aussi bien que l'octréotide 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'octréotide 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 stomatostatine comparés à ceux recevant le placebo ou non traités. L'apparition d'une hyperglycémie après application d'analogues de la somatostatine, en particulier le pasiréotide, est inquiétante. Les analogues de la somatostatine ont trouvé une application dans le traitement des cancers. Ils peuvent améliorer 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.

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

* Corresponding author. 50-556 Wroclaw, Poland.
E-mail address: mariola.sliwinska-mosson@umed.wroc.pl (M. Śliwińska-Mossoń).

http://dx.doi.org/10.1016/j.ando.2014.06.004
0003-4266/

1. Introduction

Somatostatin (SS) is a cyclic polypeptide, occurring in humans in two forms – one consisting of 14 aminoacids and the other consisting of 28 aminoacids [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