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Review

Reprint of: Metabolic effects and mechanism of action of the chromogranin A-derived peptide pancreastatin ☆

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ABSTRACT

Pancreastatin is one of the regulatory peptides derived from intracellular and/or extracellular processing of chromogranin A, the soluble acidic protein present in the secretory granules of the neuroendocrine system. While the intracellular functions of chromogranin A include formation and maturation of the secretory granule, the major extracellular functions are generation of biologically active peptides with demonstrated autocrine, paracrine or endocrine activities. In this review, we will focus on the metabolic function of one of these peptides, pancreastatin, and the mechanisms underlying its effects. Many different reported effects have implicated PST in the modulation of energy metabolism, with a general counterregulatory effect to that of insulin. Pancreastatin induces glycogenolysis in liver and lipolysis in adipocytes. Metabolic effects have been confirmed in humans. Moreover, naturally occurring human variants have been found, one of which (Gly297Ser) occurs in the functionally important carboxy-terminus of the peptide, and substantially increases the peptide's potency to inhibit cellular glucose uptake. Thus, qualitative hereditary alterations in pancreastatin's primary structure may give rise to interindividual differences in glucose and lipid metabolism. Pancreastatin activates a receptor signaling system that belongs to the seven-spanning transmembrane receptor coupled to a Gq–PLCβ–calcium–PKC signaling pathway. Increased pancreastatin plasma levels, correlating with catecholamines levels, have been found in insulin resistance states, such as gestational diabetes or essential hypertension. Pancreastatin plays important physiological role in potentiating the metabolic effects of catecholamines, and may also play a pathophysiological role in insulin resistance states with increased sympathetic activity.

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1. Introduction

Pancreastatin (PST) was isolated from porcine pancreas and was first considered as a new pancreatic peptide inhibitor of insulin secretion [1,2]. Soon after, PST was found to be produced by proteolysis of chromogranin A (CGA) [3–6], an acid glycoprotein that is present in chromaffin granules of the sympathetic adrenal system in addition to a wide range of cells in the neuroendocrine, endocrine and gastrointestinal systems [7,8]. Today, it is well known that specific proteolysis of CGA can produce a variety of regulatory peptides [9], but PST was the first known biologically active peptide to be derived from CGA [10].

PST is a peptide without homology to any family of peptides, although it shares 5 Glu with gastrin sequence and the carboxyl terminal sequence Arg-Gly-amide with vasopressin. In addition, the amidated carboxyl terminal fragment is a common feature to other neuropeptides and gastrointestinal hormones [11].

One of the biological activities of PST is the regulation of exocrine and endocrine secretion of several glands [10]. Thus, PST inhibits insulin secretion stimulated by physiologic activators such as glucose, arginine and glucagon and the pharmacological activators IBMX and sulphonylurea [1,12,13]. On the other hand, PST stimulates glucagon secretion from pancreatic α-cells both *in vivo* [14] and *in vitro* [15]. PST is an endocrine pancreatic peptide that modifies the insulin/glucagon ratio to produce a catabolic and mobilizing glucose effect. PST also inhibits pancreatic [16] and gastric [17] exocrine secretion and PTH secretion from parathyroidal cells stimulated by calcium or phorbol esters [18].

Moreover, PST has also been found to regulate glucose, lipid and protein metabolism in the liver [19] and adipose tissue [20], promoting energy expenditure and providing fuel metabolites to the system. In this article we have reviewed these metabolic effects of PST and its mechanisms of action.

2. Pancreastatin structure and formation

Variations in the PST domain of CGA have been described between the following species: porcine, bovine, rat, mouse and human [3,5,6,21]. Rat and mouse share an 88% of their sequences, whereas bovine–mouse and rat–human homologies are only a 45% and a 55%, respectively. Human PST sequence has a 71% of homology with that of porcine. These homologies are higher when the C-terminal fragment containing the biological activity of the peptide is considered (76% between human and porcine PST sequences).

PST is derived from proteolysis of the precursor CGA in different molecular forms as processing intermediates, all containing the biologically conserved active C-terminal part of the molecule. Thus, peptides of 29 aa (273–301 hCGA), 48 aa (254–301 hCGA), 92 aa (210–301 hCGA) and 186 aa (116–301 hCGA) have been found in human tumors and blood [6,22–24], and in the rat [25,26]. In human plasma, PST-52 (250–301 hCGA) and a larger species of 15–20 kDa have been shown to be the major molecular forms [27]. Moreover, phosphorylation of the precursor CGA has been correlated with the processing in different tissues, at least in bovine [28].

Proteolysis of CGA may occur both inside and outside the cell to yield pancreastatin as well as other peptides with biological activity [29–31]. The intracellular processing of PST has been fully described for bovine CGA and partially for rat CGA. The mechanism involves proteases such as pro-hormone convertase-2 (PC-2) and carboxypeptidase H [32,33]. More recently, MALDI-TOF experiments [34] documented the formation of endogenous pancreastatin-amide in hormone storage granules, and suggested particular proteolytic cleavage sites for the excision of pancreastatin from bovine CHGA. At their carboxy-termini, the cleavages are consistent with the actions of basic-residue recognizing pro-hormone convertases [35], followed by the peptide α-amidating mono-oxygenase [36]. At their amino-termini, the pancreastatin fragment masses suggested the actions of different classes of proteases, such as cathepsin L and trypsin [34,37]. In this line, cathepsin L has been found in the chromaffin granule colocalizing with CGA [38].

In humans, PST has been found to have three naturally occurring genetic variants, one of which (Gly297Ser) occurs in the functionally important carboxy-terminus of the peptide, and substantially increases the peptide's potency to inhibit cellular glucose uptake [34].

3. Metabolic effects of pancreastatin in the liver

3.1. Hepatic glycogen metabolism

PST activates glycogenolysis in the rat liver. Thus, PST increases glucose release from the liver, resulting in a hyperglycemic effect [39,40]. This effect can be observed *in vivo*, even without the modification of glucagon or insulin levels, suggesting a direct effect on liver metabolism. This observation was confirmed by studies in isolated hepatocytes, in which PST had a glycogenolytic effect similar to that of glucagon in potency, but was independent of cAMP production and dependent on calcium [41]. In fact, this glycogenolytic effect correlates with the dose-dependent increase in intracellular free calcium produced by a PST challenge [42].

In addition to its glycogenolytic effect, PST also inhibits insulin stimulated glycogen synthesis, but unlike glucagon does not affect the rate of insulin stimulated glycolysis [43]. In this way, even though the glycogenolytic effect of PST is comparable to that of glucagon, the latter produces higher levels of hyperglycemia. Conversely, PST inhibits glucagon-stimulated insulin release and thus enhances the hyperglycemic effect of glucagon.

3.2. PST regulation of cell growth

PST has been found to have an inhibitory effect on cell growth in a variety of pancreatic and hepatic cell lines. This inhibitory effect of PST has also been observed *in vivo* in islets transplanted into nude mice. Moreover, PST inhibits basal and CCK-stimulated pancreas growth in mice [44]. Consistent with this, PST can also inhibit DNA synthesis in rat fetal islets [45].

Even though PST stimulates MAPK signaling in HTC hepatoma cells, we have found that PST inhibits protein and DNA synthesis [46]. The PST-induced inhibition of cell growth observed in HTC hepatoma cells is mediated by NO production. If NO production is blocked, PST stimulates cell growth [46]. This stimulatory effect is mediated by activation of the MAPK pathway. In this way, the final effect of PST on hepatocyte growth may depend on NO availability.

4. Biological effects of PST on rat adipocytes

White adipose tissue plays a very important role in the energetic balance of mammals. This tissue is specialized to store lipids and supply fuels to the whole body when necessary. However, adipose tissue is not only a reserve organ, it is also an endocrine organ that is able to release hormones and peptides that act through autocrine, paracrine and endocrine mechanisms.

4.1. Pancreastatin regulates glucose, lipid and protein metabolism in rat adipocytes

Our results indicate that in rat adipocytes [47], PST promotes energy expenditure, with an effect that is especially relevant in preventing insulin action on energy metabolism. In this sense, PST inhibits glucose uptake by isolated adipocytes. The maximal inhibitory effect is produced by 10 nM PST with a 25% inhibition of basal glucose uptake and a 50% inhibition of insulin action. Glucose oxidation, measured as lactate production, is also affected by PST. A maximal

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