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Pancreastatin in Metabolic Diseases

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Introduction

Although studies over the years established the anti-insulin or so-called "dysglycemic" nature of the pancreastatin (PST) peptide, systematic analysis of this peptide in various human populations have not been studied. For example, one study reported the elevated levels of plasma PST in a small European population[1]. A large scale analysis in our Indian populations might assess the potential role of this peptide either as a biomarker or as an intermediate phenotype for various metabolic disorders. Five non-synonymous (R253W, A256G, E288K, G297S and R300Q) and two synonymous (G266G and G273G) variants of PST have been reported in the dbSNP database. Do these PST variants also present in Indian populations?. Systematic study on PST might have direct implications on understanding the molecular basis of action of PST and might help in drug designing, identification of therapeutic targets and therapeutic approaches. Overall, these studies would elevate the fundamental aspects of PST mediated effects on cells and human subjects and thereby, would be useful in understanding physiological manifestations.

Discovery of pancreastatin peptide

PST was first isolated from porcine pancreas in 1986[2], it gets cleaved from Chromogranin A (CHGA), a member of the granins, acidic, soluble protein that is ubiquitous in secretory cells of the nervous, endocrine system and immune system[3,4]. Pancreas[5], stomach, pituitary adenomas[6] and pancreatic acinar AR42J cells[7], endocrine tumours expresses Chromogranin A (CHGA), and can secrete PST. Plasma PST levels were significantly higher in type-2-diabetes (18.5 +/- 4.2 pmol/l) as compared to controls (4.9 +/- 0.7 pmol/l)[1]. PST diminishes glucose-stimulated insulin secretion from islet β cells. Alterations in the PST domain of CHGA were described across porcine, bovine, mouse, rat and human[8-11]. PST exists in different molecular forms and all forms contain this biologically active conserved C-terminal. 29-mer PST ($hCHGA_{273-301}$), 48-Xmer PST ($hCHGA_{254-301}$), 92-mer PST ($hCHGA_{210-301}$) and 186-mer PST ($hCHGA_{116-301}$) are present in human blood, tumors[12-14] and in rat[15,16]. PST-52 ($hCHGA_{250-301}$) is the major molecular form of PST[17].

Formation of PST

Proteolytic cleavage of CHGA generates PST and other biologically active peptides[18-20]. Proteases like pro-hormone convertase-2 and carboxypeptidase H are involved in the intracellular processing of PST[21,22]. MALDI-TOF experiments revealed the formation of PST-amide in hormone storage granules[1].

Biological effects of PST on pancreas

PST acts as an inhibitor of glucose-stimulated insulin secretion from the porcine pancreas, particularly the first phase of insulin secretion[2]. In RINm5F pancreatic cells, PST displayed significant inhibition of insulin secretion stimulated by glyceraldehydes, carbachol[23], and increase of the cytosolic Ca^{2+}[24]. PST also diminishes insulin release induced by various physiological (glucose, arginine)[25] and hormonal (VIP, GIP, CCK-8[26] and glucagon stimuli[27].

PST stimulates the secretion of amylase from the exocrine pancreas[28]. In rats, PST has an inhibitory effect on exocrine pancreatic secretion after meal, central vagal nerve stimulation and CCK-8[29]. These effects seem to be governed by presynaptic modulation of acetylcholine release from vagal system[29].

Effects of PST on gastric secretion

PST inhibits gastric acid secretion from isolated parietal cells of rabbit[30], but in vivo certainly increases gastric acid secretion in the conscious dog after meal[31]. PST inhibits parietal cell signal

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transduction through cAMP pathways[32].

PST receptor and signalling

PST receptors have been characterized from rat liver membranes [33]. The receptor is a glycoprotein, partly sensitive to pertussis toxin that can be particularly bound to different lectins, like the Wheat-germ agglutinin (WGA) lectin. PST receptor is an 80 kDa glycoprotein that is physically bound with a Gαq/11 protein [34, 35]. However, conclusive identification of the PST receptor has remained elusive so far. Adaptive UPR chaperone GRP78 (HSPA5) acts as the major hepatic target of PST and HSPA5 over-expression antagonizes PST action [36].

PST signalling in liver and adipocyte

The receptor for PST has been found to be coupled with GTP-binding proteins[37-39]. The coupling occurs in two phases. In the first phase, PST binding is sensitive to the guanine nucleotide presence. In the second phase, PST binding enhances GTPase activity and, finally, a Gαq/11 proteins have been identified with the purified PST receptor. PST has been shown to induce PLC-β activity in the rat liver membranes[40,41]. As a result of this PLC-β activation IP3 is released and intracellular calcium rapidly increases[42]. Moreover, the glycogenolytic effect of PST was observed to be cAMP-independent but highly dependent on both intracellular and extracellular calcium[43]. PST was also found to enhance cGMP production in rat hepatocytes, and is dependent on the production of nitric oxide[44].

PST increases gluconeogenesis in liver. The opposing effects of PST on insulin signalling via the Akt/FOXO-1 and SREBP1c gluconeogenic pathways are intervened by cPKC-dependent inactivation of PI3-kinase activity[45]. In addition, PST restores phosphoenolpyruvate carboxykinase-1 gene (Pepck1) and glucose-6-phosphatase (G6pase) gluconeogenic genes compared to KO mice. Thus, PST plays a major role in the gluconeogenic gene transcription regulation by insulin.

PST signalling in adipocyte

Similar to findings in the hepatocyte, PST receptor in the adipocyte is also coupled to two families of GTP-binding proteins in different proportions. Most of the coupling occurs with a G protein of the αq/11 families that impart the activation of PLC-β3 signalling pathway. On the other hand, some coupling also occurs to a G protein of the αi1,2 isoform[46]. Downstream to the PLC pathway PST enhances the amount of classical PKC. PKC inhibits glucose transport, leptin expression and glycogen synthesis, as well as the lipolyticeffect[47-49].

PST on insulin signalling

PST acts as counter regulatory peptide for insulin action; there exists a cross-talk of PST with insulin signalling in rat hepatoma cells and adipocytes. After insulin stimulation, downstream to the receptor tyrosine kinase activity, tyr-phosphorylated IRS-1 and IR is produced[50]. This insulin signalling pathway mediates stimulation of glucose uptake, glycogen and protein synthesis, lipogenesis and inhibition of lipolysis[51]. PST stimulates Ser phosphorylation of IR and IRS-1that leads to insulin resistance. PST decreases insulin-stimulated GLUT4 translocation to inhibit glucose transport.PST found to exhibit anti-insulin and lipolytic effect in white adipocytes. PST dose-dependently decreased the basal and insulin-stimulated glucose transport, lipogenesis and lactate production in adipocytes[52] PST shows lipokinetic effect, acts as an inhibitor of insulin action in rat adipocytes[52].

PST in humans

In humans, PST might be important for physiological blood glucose homeostasis and insulin, thus diabetes mellitus[53]. PST is active on glucose and free fatty acid metabolism in humans, but not on amino acid metabolism[54]. Plasma PST concentration was elevated in type-2-diabetes compared to controls, and this elevation was resistant to weight reduction[1]. PST is also elevated in hypertensive subjects[55]. Therefore, PST actions might contribute to the insulin resistance.PST levels were elevated about 3.7-fold in subjects with type-2-diabetes[1]. In the context of increased sympathetic tone (essential hypertension), release of PST was augmented[55]. PST then might trigger hepatic glycogenolysis and adipocyte lipolysis to cause insulin resistance.

Human PST natural amino acid variants discovery in Indian population

In Indian population (n=410), three genetic variants were identified: Arg253Trp, Glu287Lys, and Gly297Ser. Approximately 14% of Indian subjects had one or another of these PST amino acid variants. Both Lys-287 peptide (PST-287K) and the PST-297S peptide displayed higher potencies (than PST-WT) to various cellular events, including inhibition of insulin-stimulated glucose uptake, enhancement of nitric oxide and Ca^{2+} levels, and activation of gluconeogenic gene transcription. Consistently, the subjects with PST-297Ser allele displayed higher plasma glucose levels compared with to subjects with PST-297Gly allele. Interestingly, the PST-297S and PST-287K peptides showed higher helical content than the PST-WT peptide, suggesting that the gain of potency for these variant peptides may be due to their more ordered structures[56].

PST inhibitor and future perspectives

PSTi8 (PEGKGEQEHSQQKEEEEEMAV-amide) is a pancreastatin inhibitor peptide with potent antidiabetic activity in type 2 diabetic mice. PSTi8 also suppressed PST- induced insulin resistance in liver cells. PSTi8 administration increased insulin sensitivity in peri-/post-menopausal rats with insulin resistance, signalling is mediated through either IRS1-2-phosphatidylinositol-3-kinase-AKT-GSK3βorIRS1-2-phosphatidylinositol-3-kinase-PKCλ/ζ-SREBP1c in the liver. Thus, PSTi8 can act as a potential therapeutic peptide for the treatment of peri-/post-menopausal IR[57]. More research on PST inhibitors will open new avenues in the potential therapy for treatment diabetes and metabolic diseases[58].

Conflicts of Interest

The author has no conflicts of interest to report.

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