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Pancreastatin

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1. General

Pancreastatin (PST) was first isolated from pig pancreas by Tatemoto et al as a result of screening for peptides with a C-terminal amide structure that is common to neuropeptides and peptide hormones and was shown to inhibit stimulated insulin secretion (43). Shortly thereafter PST was also shown to inhibit exocrine pancreatic secretion (10, 28).While porcine PST is a 49 amino acid peptide, the biological activity resides in the carboxyl half and requires the C-terminal glycine-amide. PST has been subsequently identified as a protein or from cDNA sequences from other species showing homology but in some have extra amino acids; human PST has 52 amino acids. These proteins as well as the C-terminal portion have been synthesized and shown to inhibit insulin secretion (10, 27).

PST is derived from chromogranin A (CGA), an acidic protein originally isolated from the chromaffin cells of the adrenal medulla where it is present in secretory granules as a packaging protein (16). PST was recognized in the cDNA sequence of bovine, porcine, human and rat CGA (19, 20, 25, 30). Human CGA has 439 aa and human PST is residues 250-301. Chromogranins are now known to possess a variety of other biologically active peptides including a variety of antimicrobial peptides (16, 40). Chromogranin contains ten dibasic cleavage sites and prohormone convertase-1 is required for production of PST (44). PST has been identified by immunohistochemistry in a number of endocrine cells in the pancreas, gut, pituitary, and adrenal medullae that are all known to contain CGA (23, 33, 41). Chromogranin A has long been known to be secreted by the adrenal medulla (3) and PST can be measured in plasma (24). Recently plasma levels of PST have been used as a predictive marker for neuroendocrine tumors where PST is elevated (31, 34); in normal humans the plasma level is 20-80 pg/ml or about 4-20 pM (34, 42). In the pancreas, PST colocalizes with all four major endocrine cell types (4, 40). PST is released in parallel with insulin from the perfused porcine pancreas (32). Thus PST could have effects on both pancreatic endocrine and

exocrine cells by an autocrine or paracrine mechanism or through the islet-acinar portal system.

In addition to effects in the pancreas discussed below, PST has metabolic effects in liver, adipose tissue and heart (36, 45). Many of these effects are anti-insulin such as inhibition of gluconeogenesis and activation of glycogenolysis in hepatocytes and inhibition of glucose uptake in fat cells. Specific PST binding proteins (receptors ?) have been characterized by radioligand binding and cross-linking in liver, heart and adipose tissue membranes (14, 15, 38) although the receptor has not yet been cloned. The presumptive receptors belong to the G protein coupled family and interact with $G_{q/11}$ and G_i proteins (37, 39). The $G_{q/11}$ protein couples to PLCβ3 and thereby increases intracellular Ca^{2+} and activates classical forms of PKC. The G_i proteins mediate inhibition of hepatocyte cell growth through activation of nitric oxide synthase (NOS) and production of cyclic GMP (5, 35, 36). In rat adipocytes, PST also activates the protein synthesis pathway (13). Direct binding of PST to the heat shock protein, GRP78 (glucose regulated protein of 78 kilodalton) in liver homogenate has also been demonstrated (2). PST inhibited GRP78's ATPase activity which is required for action as a chaperone. This was suggested to influence insulin binding and signal transduction.

2. Role of pancreastatin in the pancreas

Endocrine Pancreas

In the original study identifying PST, both intact and C-terminal 16 amino acid porcine peptide inhibited insulin secretion (43). In a follow up study the same group showed in the perfused rat pancreas that PST at 1 and 10 nM inhibited both first and second phase insulin secretion stimulated by glucose or arginine, had a small effect to reduce somatostatin secretion and enhanced glucagon secretion stimulated by arginine or low glucose (7). The shortest C-terminal peptide showing full inhibition of insulin secretion was PST 35-49 (48). Subsequent studies have confirmed the PST inhibition of insulin secretion in both rats and mice in vivo, using the perfused pancreas and in isolated islets (1, 21, 28, 29, 47). In some studies the effect was seen at 20 or 200 pM but most studies used higher doses (46). Effects on glucagon secretion have not been as consistent as on insulin secretion. Whether these effects are of physiological importance is still unclear. The in vitro studies suggest a direct effect but have not yet been related to the presence of a specific receptor on beta cells. Plasma levels of PST are increased in Type 2 diabetes but this may simply reflect increased beta cell secretion. Gene deletion studies on CGA have been interpreted as showing an important role of PST on glucose homeostasis (12) but deletion of CGA has multiple effects on the animal many of which are probably not related to PST. Recently, a PST peptide with the eight carboxy terminal amino acids deleted termed PSTi8 has been shown to bind to PST receptors and inhibit the metabolic effects of PST and improve the glucose status in rodent models of diabetes (18).

Exocrine Pancreas

Along with the inhibition of insulin secretion, multiple natural and synthetic forms of PST (human, porcine, bovine, rat) have been shown to inhibit pancreatic digestive enzyme

secretion stimulated by a meal, diversion of bile-pancreatic juice, or administration of CCK in vivo in rats (8-10, 17, 28, 29) and dogs (6). PST also inhibited pancreatic exocrine secretion stimulated by 2-deoxy-D-Glucose, a central vagal activator. By contrast to CCK, pancreatic exocrine secretion stimulated by the cholinergic analog bethanachol in vivo was not blocked by PST (17). Studies of isolated rat pancreatic acini showed no consistent inhibitory action of PST on CCK stimulation (6, 11, 17, 29) although there is one report of inhibition of CCK stimulation in guinea pig acini (21). Because PST inhibited exocrine pancreatic secretion in vivo but not by isolated cells, the effect of PST is presumed to be indirect.

One possible site of action is on pancreatic blood flow as shown in anesthetized rats using the hydrogen clearance method (26). These investigators found that caerulein enhanced pancreatic blood flow and this increase was dose dependently inhibited by PST at 100 to 500 pmol/kg per h. However, in another study in anesthetized dogs using the laser Doppler flowmeter method, no effect of PST was observed at similar concentrations although protein and amylase secretion were inhibited (6). The other possible site is on the neural stimulatory pathway. Herzig et al. showed that when pancreatic lobules, which contained neural elements, were incubated in vitro, high K^+ concentrations stimulated the release of acetylcholine and amylase secretion; both of which were partially inhibited by PST (17). Further studies are necessary to establish pancreastatin as a regulatory peptide on the exocrine pancreas and to follow up these potential echanisms of action. It is also not clear whether PST from a pancreatic or systemic source plays a physiological role in the regulation of exocrine pancreatic function. Absent at present is any information about a PST receptor molecule or PST sensitive ion channel in the pancreas. Moreover, it is not clear what is a physiological concentration of PST.

3. Tools for the study of Pancreastatin

a. Antibodies

Biocompare lists 968 antibodies to PST but many of these are to CGA. The only useful antibodies are those that react with PST and not CGA and this is best achieved by immunization with a synthetic carboxy terminal of PST so part of the immunogen is not present in CGA. Such antibodies have been characterized and used for RIA of plasma PST (31, 42). All antibodies to PST need to be characterized for the particular technique being used (22).

b. Inhibitors

Recently, the peptide PEGKGEQEHSQQKEEEEEMAV-amide has been reported to act as an inhibitor of the peripheral metabolic action of PST (18).

4. References:

1. **Ahren B, Lindskog S, Tatemoto K, and Efendic S**. Pancreastatin inhibits insulin secretion and stimulates glucagon secretion in mice. *Diabetes* 37: 281-285, 1988. PMID: 3286328

2. **Biswas N, Friese RS, Gayen JR, Bandyopadhyay G, Mahata SK, and O'Connor DT**. Discovery of a novel target for the dysglycemic chromogranin A fragment pancreastatin: interaction with the chaperone GRP78 to influence metabolism. *PLoS One* 9: e84132, 2014. PMID: 24465394
3. **Blaschko H, Comline RS, Schneider FH, Silver M, and Smith AD**. Secretion of a chromaffin granule protein, chromogranin, from the adrenal gland after splanchnic stimulation. *Nature* 215: 58-59, 1967. PMID: 6053402
4. **Bretherton-Watt D, Ghatei MA, Bishop AE, Facer P, Fahey M, Hedges M, Williams G, Valentino KL, Tatemoto K, Roth K, and et al.** Pancreastatin distribution and plasma levels in the pig. *Peptides* 9: 1005-1014, 1988. PMID: 3244555
5. **Diaz-Troya S, Najib S, and Sanchez-Margalet V**. eNOS, nNOS, cGMP and protein kinase G mediate the inhibitory effect of pancreastatin, a chromogranin A-derived peptide, on growth and proliferation of hepatoma cells. *Regul Pept* 125: 41-46, 2005. PMID: 15582712
6. **Doi R, Inoue K, Hosotani R, Higashide S, Takaori K, Funakoshi S, Yajima H, Rayford PL, and Tobe T**. Effects of synthetic human pancreastatin on pancreatic secretion and blood flow in rats and dogs. *Peptides* 12: 499-502, 1991. PMID: 1717953
7. **Efendic S, Tatemoto K, Mutt V, Quan C, Chang D, and Ostenson CG**. Pancreastatin and islet hormone release. *Proc Natl Acad Sci U S A* 84: 7257-7260, 1987. PMID: 2890162
8. **Funakoshi A, Miyasaka K, Kitani K, Funakoshi S, Tamamura H, Fujii N, Nakano I, and Tatemoto K**. Comparative effects of mammalian pancreastatins on the pancreatic exocrine secretion. *Jpn J Physiol* 39: 901-905, 1989. PMID: 2632902
9. **Funakoshi A, Miyasaka K, Kitani K, and Tatemoto K**. Effect of pancreastatin on pancreatic endocrine function in the conscious rat. *Regul Pept* 24: 225-231, 1989. PMID: 2652201
10. **Funakoshi A, Miyasaka K, Nakamura R, Kitani K, Funakoshi S, Tamamura H, Fujii N, and Yajima H**. Bioactivity of synthetic human pancreastatin on exocrine pancreas. *Biochem Biophys Res Commun* 156: 1237-1242, 1988. PMID: 3190702
11. **Funakoshi A, Miyasaka K, Nakamura R, Kitani K, and Tatemoto K**. Inhibitory effect of pancreastatin on pancreatic exocrine secretion in the conscious rat. *Regul Pept* 25: 157-166, 1989. PMID: 2474177
12. **Gayen JR, Saberi M, Schenk S, Biswas N, Vaingankar SM, Cheung WW, Najjar SM, O'Connor DT, Bandyopadhyay G, and Mahata SK**. A novel pathway of insulin sensitivity in chromogranin A null mice: a crucial role for pancreastatin in glucose homeostasis. *J Biol Chem* 284: 28498-28509, 2009. PMID: 19706599
13. **Gonzalez-Yanes C, and Sanchez-Margalet V**. Pancreastatin, a chromogranin A-derived peptide, activates protein synthesis signaling cascade in rat adipocytes. *Biochem Biophys Res Commun* 299: 525-531, 2002. PMID: 12459169
14. **Gonzalez-Yanes C, Santos-Alvarez J, and Sanchez-Margalet V**. Characterization of pancreastatin receptors and signaling in adipocyte membranes. *Biochim Biophys Acta* 1451: 153-162, 1999. PMID: 10446397
15. **Gonzalez-Yanes C, Santos-Alvarez J, and Sanchez-Margalet V**. Pancreastatin, a chromogranin A-derived peptide, activates Galpha(16) and phospholipase C-beta(2) by interacting with specific receptors in rat heart membranes. *Cell Signal* 13: 43-49, 2001. PMID: 11257446
16. **Helle KB, Metz-Boutigue MH, Cerra MC, and Angelone T**. Chromogranins: from discovery to current times. *Pflugers Arch* 470: 143-154, 2018. PMID: 28875377
17. **Herzig KH, Louie DS, Tatemoto K, and Chung OY**. Pancreastatin inhibits pancreatic enzyme secretion by presynaptic modulation of acetylcholine release. *Am J Physiol* 262: G113-117, 1992. PMID: 1370747
18. **Hossain Z, Valicherla GR, Gupta AP, Syed AA, Riyazuddin M, Chandra S, Siddiqi MI, and Gayen JR**. Discovery of pancreastatin inhibitor PSTi8 for the treatment of insulin resistance and diabetes: studies in rodent models of diabetes mellitus. *Sci Rep* 8: 8715, 2018. PMID: 29880906
19. **Iacangelo A, Okayama H, and Eiden LE**. Primary structure of rat chromogranin A and distribution of its mRNA. *FEBS Lett* 227: 115-121, 1988. PMID: 2828116

20. **Iacangelo AL, Fischer-Colbrie R, Koller KJ, Brownstein MJ, and Eiden LE**. The sequence of porcine chromogranin A messenger RNA demonstrates chromogranin A can serve as the precursor for the biologically active hormone, pancreastatin. *Endocrinology* 122: 2339-2341, 1988. PMID: 2834189
21. **Ishizuka J, Asada I, Poston GJ, Lluis F, Tatemoto K, Greeley GH, Jr., and Thompson JC**. Effect of pancreastatin on pancreatic endocrine and exocrine secretion. *Pancreas* 4: 277-281, 1989. PMID: 2471966
22. **Ito T, Igarashi H, and Jensen RT**. Serum pancreastatin: the long sought universal, sensitive, specific tumor marker for neuroendocrine tumors? *Pancreas* 41: 505-507, 2012. PMID: 22504376
23. **Jensen TB, Fahrenkrug J, and Sundler F**. Immunocytochemical localisation of pancreastatin and chromogranin A in porcine neuroendocrine tissues. *Regul Pept* 36: 283-297, 1991. PMID: 1725220
24. **Kitayama N, Tateishi K, Funakoshi A, Miyasaka K, Shimazoe T, Kono A, Iwamoto N, and Matsuoka Y**. Pancreastatin molecular forms in normal human plasma. *Life Sci* 54: 1571-1578, 1994. PMID: 8196476
25. **Konecki DS, Benedum UM, Gerdes HH, and Huttner WB**. The primary structure of human chromogranin A and pancreastatin. *J Biol Chem* 262: 17026-17030, 1987. PMID: 2445752
26. **Migita Y, Nakano I, Goto M, Ito T, and Nawata H**. Effect of pancreastatin on cerulein-stimulated pancreatic blood flow and exocrine secretion in anaesthetized rats. *J Gastroenterol Hepatol* 14: 583-587, 1999. PMID: 10385069
27. **Miyasaka K, Funakoshi A, Kitani K, Tamamura H, Fujii N, and Funakoshi S**. The importance of the C-terminal amide structure of rat pancreastatin to inhibit pancreatic exocrine secretion. *FEBS Lett* 263: 279-280, 1990. PMID: 2335229
28. **Miyasaka K, Funakoshi A, Nakamura R, Kitani K, Shimizu F, and Tatemoto K**. Effects of porcine pancreastatin on postprandial pancreatic exocrine secretion and endocrine functions in the conscious rat. *Digestion* 43: 204-211, 1989. PMID: 2612743
29. **Miyasaka K, Funakoshi A, Yasunami Y, Nakamura R, Kitani K, Tamamura H, Funakoshi S, and Fujii N**. Rat pancreastatin inhibits both pancreatic exocrine and endocrine secretions in rats. *Regul Pept* 28: 189-198, 1990. PMID: 1693005
30. **Nakano I, Funakoshi A, Miyasaka K, Ishida K, Makk G, Angwin P, Chang D, and Tatemoto K**. Isolation and characterization of bovine pancreastatin. *Regul Pept* 25: 207-213, 1989. PMID: 2756155
31. **O'Dorisio TM, Krutzik SR, Woltering EA, Lindholm E, Joseph S, Gandolfi AE, Wang YZ, Boudreaux JP, Vinik AI, Go VL, Howe JR, Halfdanarson T, O'Dorisio MS, and Mamikunian G**. Development of a highly sensitive and specific carboxy-terminal human pancreastatin assay to monitor neuroendocrine tumor behavior. *Pancreas* 39: 611-616, 2010. PMID: 20124939
32. **Ostenson CG, Efendic S, and Holst JJ**. Pancreastatin-like immunoreactivity and insulin are released in parallel from the perfused porcine pancreas. *Endocrinology* 124: 2986-2990, 1989. PMID: 2656247
33. **Ravazzola M, Efendic S, Ostenson CG, Tatemoto K, Hutton JC, and Orci L**. Localization of pancreastatin immunoreactivity in porcine endocrine cells. *Endocrinology* 123: 227-229, 1988. PMID: 2898359
34. **Rustagi S, Warner RR, and Divino CM**. Serum pancreastatin: the next predictive neuroendocrine tumor marker. *J Surg Oncol* 108: 126-128, 2013. PMID: 23775817
35. **Sanchez-Margalet V, Gonzalez-Yanes C, and Najib S**. Pancreastatin, a chromogranin A-derived peptide, inhibits DNA and protein synthesis by producing nitric oxide in HTC rat hepatoma cells. *J Hepatol* 35: 80-85, 2001. PMID: 2445752
36. **Sanchez-Margalet V, Gonzalez-Yanes C, Najib S, and Santos-Alvarez J**. Metabolic effects and mechanism of action of the chromogranin A-derived peptide pancreastatin. *Regul Pept* 161: 8-14, 2010. PMID: 20184923
37. **Sanchez-Margalet V, Lucas M, and Goberna R**. Pancreastatin action in the liver: dual coupling to different G proteins. *Cell Signal* 8: 9-12, 1996. PMID: 8777144

38. **Sanchez-Margalet V, Valle M, and Goberna R**. Receptors for pancreastatin in rat liver membranes: molecular identification and characterization by covalent cross-linking. *Mol Pharmacol* 46: 24-29, 1994. PMID: 8058054
39. **Santos-Alvarez J, Gonzalez-Yanes C, and Sanchez-Margalet V**. Pancreastatin receptor is coupled to a guanosine triphosphate-binding protein of the G(q/11)alpha family in rat liver membranes. *Hepatology* 27: 608-614, 1998. PMID: 9462664
40. **Schmidt WE, and Creutzfeldt W**. Pancreastatin--a novel regulatory peptide? *Acta Oncol* 30: 441-449, 1991. PMID: 1854501
41. **Schmidt WE, Siegel EG, Lamberts R, Gallwitz B, and Creutzfeldt W**. Pancreastatin: molecular and immunocytochemical characterization of a novel peptide in porcine and human tissues. *Endocrinology* 123: 1395-1404, 1988. PMID: 3042370
42. **Tateishi K, Kitayama N, Matsuoka Y, and Funakoshi A**. Comparison of chromogranin A and pancreastatin levels in plasma of patients with pancreatic islet cell tumor. *Life Sci* 57: 889-895, 1995. PMID: 7630318
43. **Tatemoto K, Efendic S, Mutt V, Makk G, Feistner GJ, and Barchas JD**. Pancreastatin, a novel pancreatic peptide that inhibits insulin secretion. *Nature* 324: 476-478, 1986. PMID: 3537810
44. **Udupi V, Lee HM, Kurosky A, and Greeley GH, Jr.** Prohormone convertase-1 is essential for conversion of chromogranin A to pancreastatin. *Regul Pept* 83: 123-127, 1999. PMID: 10511466
45. **Valicherla GR, Hossain Z, Mahata SK, and Gayen JR**. Pancreastatin is an endogenous peptide that regulates glucose homeostasis. *Physiol Genomics* 45: 1060-1071, 2013. PMID: 24064537
46. **von Schonfeld J, and Muller MK**. The effect of pancreastatin on endocrine and exocrine pancreas. *Scand J Gastroenterol* 26: 993-999, 1991. PMID: 1947780
47. **von Schonfeld J, Muller MK, Runzi M, Geling M, Neisius I, Kleimann J, and Goebell H**. Pancreastatin--a mediator in the islet-acinar axis? *Metabolism* 42: 552-555, 1993. PMID: 8492708
48. **Zhang T, Mochizuki T, Kogire M, Ishizuka J, Yanaihara N, Thompson JC, and Greeley GH, Jr.** Pancreastatin: characterization of biological activity. *Biochem Biophys Res Commun* 173: 1157-1160, 1990. PMID: 2268319