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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).

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