Review

Effects of insulin and glucose metabolism on pancreatic exocrine function

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Abstract

Glucose metabolism is highly dependent on hormones secreted by the islets of Langerhans, and most notably on insulin. Moreover, the endocrine and exocrine pancreas has a complex anatomical and functional interaction. The exocrine part of the pancreas is influenced by the islet hormones mainly through an islet-acinar portal system, for example, the periinsular acinar cells are larger and contain more zymogen and amylase. The insulo-acinar axis is also indicated by morphological evidences. Hypoinsulinemia causes pancreatic atrophy with fat replacement of the exocrine pancreas in different species. These results indirectly show the significant role of insulin on pancreatic exocrine function. However, direct evidence is also available to highlight the key role of insulin. Both endogenous and exogenous insulin evoke increases in pancreatic enzyme synthesis and growth. Insulin is not only important in healthy conditions, but is also involved in the regenerative processes during pancreatitis. Human studies have also proved the necessity of insulin in pancreatic exocrine function. In conclusion, insulin has long term effects on the regulation of the biosynthesis of pancreatic digestive enzymes and short term effects on the stimulation of pancreatic secretion. Other peptides, such as pancreatic polypeptide, glucagon and somatostatin seem to inhibit pancreatic secretion, although more experiments are needed to clarify this hypothesis. Despite our current knowledge, many other hypotheses and questions remained unanswered concerning the effects of hormones secreted by different cells of the islets of Langerhans, therefore, it seems to be of great importance to explore the effects of these hormones on pancreatic exocrine function.

Key words: pancreas, diabetes, insulin, exocrine function, pancreatitis

The endocrine and exocrine pancreas has a complex anatomical and functional interaction.[1] It is well documented, that intact islets of Langerhans is necessary for the normal pancreatic exocrine function.[2,3] Moreover, the exocrine pancreas is influenced by the islet hormones not only systemically but also through a direct islet-acinar portal system.[4] The insulo-acinar axis is also indicated by other morphological evidences. The acinar cells around the islets, termed periinsular acini, can be distinguished from teleinsular acini by their histological characteristics. These periinsular cells are bigger in size, contain larger nuclei and nucleoli, and have more abundant zymogen granules[5,6,7] and amylase.[8] This heterogeneity of the acinar cells plays an important role in non-parallel secretion and adaptation of pancreatic secretion to the carbohydrate rich diet.[9] In this review key roles of insulin and normal glucose level on pancreatic exocrine function are highlighted.

The effect of insulin on the exocrine pancreas in normal condition
Effects of insulin on acinar tissue
It is well documented that both pancreatic secretory processes

and pancreatic growth are (at least partially) under the control of islet hormones. Hypoinsulinemia causes pancreatic atrophy and fat infiltration of the exocrine pancreas in guinea pigs.[10] In contrast both endogenous and exogenous insulin evoke an increase in pancreatic growth and enzyme synthesis.[11,12] The direct (via acinar insulin receptors) and indirect (influence on cholecystokinin (CCK) mechanism) effects of insulin are well characterized. Sankaran *et al.*[13] demonstrated that the binding of insulin to its receptors on pancreatic acini correlated with the subsequent stimulation of protein synthesis. Moreover, both the number of CCK receptors and their affinity was reduced in experimental diabetes.[11,14] Lee *et al.*[15] reported that an anti-insulin serum completely blocked the CCK-stimulated pancreatic secretion in rats. Another observation has also proved that endogenous insulin is necessary for the stimulatory action of CCK on pancreatic exocrine secretion and growth. Taken together, these results clearly indicate the importance of insulin in pancreatic exocrine function. Moreover, both exogenous and endogenous insulin can stimulate the acinar secretory process. Intravenous infusion of glucose stimulated pancreatic exocrine secretion indirectly, and this was inhibited by galanine.[16]

Besides the results of animal studies, some clinical research has also showed the necessity of insulin in pancreatic exocrine function. Kim *et al.*[17] investigated the effects of endogenous insulin on pancreatic exocrine secretion in humans, by

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evaluating pure pancreatic juice obtained by endoscopic cannulation of the main pancreatic duct. After infusion of glucose, plasma insulin and C-peptide levels were significantly elevated and remained high during the 30-min experiment, while repeated intravenous administration of secretin and CCK resulted in a significant increase in pancreatic secretion including bicarbonate and protein output as compared to the response without glucose pretreatment. The observations suggest that endogenous insulin intensifies pancreatic secretion stimulated by secretin and CCK in humans. In type 1 diabetes, the pancreas is usually atrophied with increased fibrosis and fatty infiltration.[18] In addition to this, a high incidence of pancreatic dysfunction has been observed in insulin dependent diabetes mellitus.[19]

Effects of insulin on pancreatic ducts

Interestingly enough, exogenous insulin may have an opposite effect on pancreatic fluid and bicarbonate secretion. The bicarbonate ions found in the pancreatic juice are secreted by duct cells.[20,21] This alkaline secretion washes out digestive enzymes along the ductal tree into the duodenum, and also contributes to the neutralization of acid chyme entering the duodenum from the stomach.[20,22] Exogenous insulin inhibits secretin-stimulated pancreatic bicarbonate output in a dose-dependent manner in dogs, and this effect can be inhibited by pancreatic denervation. It has also been confirmed that cholinergic mechanisms mediate the insulin exerted inhibition of secretin-induced pancreatic bicarbonate output.[23,24] In contrast, some human studies suggest, that the inhibitory effect of hyperglycemia on pancreaticobiliary secretion may occur independently of insulin.[25,26] Lam et al[27] found that during both acute hyperglycemia and euglycemic hyperinsulinemia, basal pancreatic secretion was significantly reduced. However, CCK-stimulated pancreatic enzyme output was significantly reduced only during hyperglycemia.[27]

The role of insulin in the exocrine pancreas secretion in pathological conditions
Diabetes mellitus

In streptozotocin-diabetic rats (without pancreatitis) the pancreatic enzyme show a decrease in amylase and an increase in trypsinogen activities.[7] These data are in accordance with those of Sofrankova et al,[28] who demonstrated similar pancreatic enzyme patterns in a previous secretory study. These facts indicate a role of insulin in the trophic effect (with or without CCK) on the exocrine pancreas of normal rats. Additionally, with respect to the concerns of the endocrine function in streptozotocin-diabetic rats, low doses of CCK resulted in further elevations of serum glucose levels.[28] This additional hyperglycemia might be due to an increase in pancreatic amylase secretion in response to CCK, which possibly contributes to increased digestion of polysaccharides. These chronically high blood glucose levels seem to exhaust the pancreatic β-cells and appear to cause further reduction in the number of surviving β-cells.[29]

Pancreatitis

The role of insulin in the process of pancreatic regeneration following acute pancreatitis has been recently demonstrated by Hegyi et al, [29,30] using the arginine-induced pancreatitis model, which seems to be a suitable model for studying the correlation between diabetes and pancreatitis.[31,32,33,34] The advantage of the arginine-induced pancreatitis model is that it is non-invasive, highly reproducible, producing selective acinar cell necrosis in rats.[35] The interesting finding that the periinsular acini remained intact during arginine-induced-pancreatitis prompted this team to continue with studies on the effects of diabetes in the process of pancreatic remodeling.[36] While the intact islet cells exerted a protective effect mainly on the periinsular acini in this experimentally-induced pancreatitis, in the diabetic animals, the regeneration also was inhibited after pancreatitis. When diabetic rats without pacreatitis were injected with physiological doses of CCK, no significant changes in pancreatic DNA or enzyme content were observed contrary to the findings in control animals. In diabetic rats with pancreatitis, the pancreatic regenerative processes (also mitotic activity of acinar cells) in response to low doses of CCK were markedly diminished.[37] These findings underline the importance of the close anatomic and functional relationship between the endocrine and exocrine pancreas.[38,39] Otsuki et al[40] also reported that the effects of CCK on the pancreatic acinar cells was significantly reduced in experimental diabetes. It seems likely that the lower sensitivity to CCK is due to an impaired ability of receptor-bound CCK to initiate an appropriate cellular response. The reduction in the tropic effect of CCK may be due to the low insulin level. Moreover, there was no significant difference between the peri- and teleinsular acinar cell damage in these diabetic rats.[40] This provides morphological confirmation of the key role of insulin in the regulation of the whole exocrine pancreatic structure. However, it is important to note that other islet cell hormones, for example glucagon, and somatostatin may also be involved in this process.[7,41] The reduced insulin level significantly influences secretory patterns of the exocrine pancreas.[41] Basal and CCK-stimulated fluid and amylase secretions are reduced in diabetes.[42] Furthermore, while increases can be observed in the basal pancreatic fluid and amylase secretions in diabetic and pancreatitic rats, there was no CCK-stimulated fluid secretory peak detected following pancreatitis in diabetic animals, which contrasts with the situation in non-diabetic rats.[42]

Finally, exogenous replacement of insulin directly proved the important role of insulin in the function of exocrine pancreas. In the diabetic-pancreatitic rats treatment with insulin and CCK significantly elevated the pancreatic contents of protein, amylase and lipase compared to those rats that received only CCK treatment. Moreover, CCK administered in combination with insulin also elevated the number of mitotically active acinar cells, whereas CCK alone had no effect on laboratory parameters or on the mitotic activity in the diabetic-pancreatitic rats.[43,44]

The role of other islet peptides in the pancreatic exocrine function

It is well documented that the islets of Langerhans contain not only ß cells, but also glucagon-producing-a cells, somatostatin-producing d cells and pancreatic polypeptide producing (PP) cells.[45,46] These hormones can regulate ß cells secretion, thus they can directly modify plasma insulin levels.[47,48] However, specific somatostatin receptors have been identified on acinar cells, and somatostatin was found to inhibit the basal and stimulated pancreatic secretion.[49-53] The effect of glucagon is more confusing. *In vivo* glucagon inhibited CCK and secretin stimulated secretion in dogs and rats, however, *in vitro* glucagon has been reported to stimulate the secretion.[54,55] There has been very little advance in knowledge concerning the effect of pancreatic polypeptide (PP). *In vivo* administration of pancreatic polypeptide inhibits CCK-stimulated pancreatic secretion.[56,57] Contrary to this, *in vitro* experiments have shown no inhibition of stimulated secretion of the pancreas.[58] Moreover, PP could stimulate DNA synthesis acinar cells in culture, and therefore, it appears to have a positive effect on acinar tissue.[59]

At present it is difficult to conclude how much these islet hormones by themselves have an effect on the pancreatic exocrine function besides their indirect influence through the insulin release and glucose metabolism.

Conclusions

The degree of insulo-acinar interaction has already been suggested several years ago, however, the complex effects of insulin on pancreatic secretion have not been described so far. Most articles focused on the effects of insulin indirectly usually describing the disadvantage of insulin shortage. However, in the experiments where exogenous insulin was also administered, the key role of the hormone was directly proven. Insulin has long-term effects on the regulation of the biosynthesis of pancreatic digestive enzymes and short term effects on the stimulation of pancreatic secretion in physiological and disease state. Concerning the other peptides, PP, glucagon and somatostatin seem mainly to inhibit pancreatic secretion, but much more work is needed to clarify the mechanisms. There are many questions, which remained to be answered regarding the effects of hormones secreted by different islet cells, on exocrine pancreatic function, digestion, nutritional state and metabolism.

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