Beneficial effects of physical exercise on the exocrine pancreas

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Received: August 3, 2015 / Accepted: August 17, 2015

Abstract The pancreas is a retroperitoneal organ critically important for intestinal digestion. Most of the pancreas consists of exocrine glands that synthesize and secrete a great majority of digestive enzymes into the pancreatic duct tributaries and on into the duodenum. It also contains important endocrine glands that produce hormones such as insulin, glucagon, and somatostatin, thus also regulating nutrition and gastrointestinal function. Since the exocrine pancreas serves a central and essential role in the digestive process, its dysfunction may result in malabsorption and malnutrition. Previous studies have shown that exocrine pancreatic dysfunction could be induced by various physical conditions such as obesity, diabetes, and aging. In addition, food consumption and dietary components have been reported to affect pancreatic enzyme synthesis and secretion. However, little is known about the effects of physical exercise on the function of the exocrine pancreas. This review focuses on the effects of physical exercise on functional and ultrastructural alterations in the exocrine pancreas. Furthermore, the importance of physical exercise on exocrine pancreas dysfunction is discussed.

Keywords: exocrine pancreas, exercise, electron microscopy, ultrastructure

Introduction The pancreas is a mixed gland, which has both exocrine and endocrine compartments. It is a retroperitoneal organ that lies transversely behind and below the stomach, located between the loop of the duodenum and the hilum of the spleen. The exocrine compartment, comprising about 90% to 95% of the mass of the pancreas, consists of grapelike clusters of acinar cells that form acini, which connect to ducts that eventually empty into the duodenum. The endocrine pancreas, comprising about 2% of the mass of the pancreas, consists of small aggregations of cells, known as the islets of Langerhans, which are irregularly scattered throughout the exocrine pancreas cells, pervaded by a dense network of capillaries (Fig. 1). Such a unique arrangement of the endocrine compartment dispersed as islets within the exocrine pancreas seems to imply a relationship between the endocrine and exocrine pancreas. In fact, streptozotocin-induced diabetic rats showed functional reduction in the exocrine compartment of the pancreas. Also it has been reported that exocrine insufficiency is clinically closely associated with insulin-dependent diabetic patients. Therefore, it could be pointed out that there are important interrelationships between the endocrine and exocrine pancreas. Although exercise or diet therapy has been recommended for prevention of endocrine dysfunction, studies concerning the effects of exercise on exocrine pancreatic insufficiency are scarce. Thus, the aim of this review is to demonstrate the effects of physical exercise on exocrine pancreatic function and ultrastructure of the exocrine pancreas.

Structure of the exocrine pancreas The pancreas plays dual physiological roles as both an exocrine gland for digestion and nutrition and an endocrine gland for glucose homeostasis. The exocrine pancreas is a compound tubuloalveolar gland comprised of acinar cells arranged in glands, and a network of ducts that transport digestive enzymes secreted by acinar cells into the duodenum of the gastrointestinal tract. Therefore, the exocrine pancreas secretes digestive juice, which is a clear alkaline digestive fluid, composed of digestive enzymes secreted by acinar cells into the duodenum. This alkaline digestive juice neutralizes the hydrochloric acid from the stomach and provides the optimal conditions for the digestive enzymes to function properly. These digestive enzymes are responsible for a major part of chemical digestion in the small intestine.

Fine structure of the acinar cells The exocrine pancreas consists of a heterogeneous arrangement of acinar units composed of a cluster of acinar cells. Ultrastructural observations of the acinar cell (Fig. 2) reveals many intracellular constituents essential for the synthesis, packaging, and release of digestive enzymes. The nucleus of the acinar cell is located in the periphery, which frequently displays a prominent nucleolus and both
Duct cells secrete aqueous NaHCO$_3$ solution

Acinar cells secrete digestive enzymes

Exocrine portion of pancreas (Acinar and duct cells)

Endocrine portion of pancreas (Islets of Langerhans)

The glandular portions of the pancreas are grossly exaggerated.

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**Fig. 1** Diagrammatic representation of the exocrine and endocrine compartments of the pancreas (cited from literature).
euchromatin and heterochromatin. The basal region of the acinar cell is filled with layers of rough endoplasmic reticulum surrounding the nucleus. The multiple protein enzymes are synthesized by ribosomes associated with the outer surfaces of the cisternal membranes and inserted into the lumen of the rough endoplasmic reticulum. The synthesized protein enzymes are then transported to the Golgi apparatus located in the supranuclear region, via small membranous transition vesicles. The major function of the Golgi apparatus in the exocrine pancreas is to package the protein enzymes into condensing vacuoles, which contain precursors of the digestive enzymes, and finally concentrate the condensing vacuoles into mature zymogen granules. Each zymogen granule is surrounded by a membrane containing multiple digestive enzymes until secretion is initiated. The electron-dense zymogen granules occupy the apical region of the acinar cell.

Upon stimulation of secretion, the zymogen granule membrane fuses with the apical plasma membrane of the acinar cell. The contents of the zymogen granules are thereby discharged by exocytosis into the acinar lumen, which is continuous with the intercalated duct. Such ultrastructural features of the acinar cell demonstrate its specialized ability to synthesize, store and secrete digestive enzymes.

The ability of the exocrine acinar cells to synthesize and secrete proteins, mainly digestive enzymes, is greater than any other tissue. Therefore, in humans, the exocrine pancreas is able to deliver 6-20 g of digestive enzymes each day to the duodenum in about 2 liters of digestive juice.

Regulation of exocrine pancreatic secretion

Exocrine pancreatic secretion is regulated by a number of factors that are part of the response to food in the gastrointestinal tract. The predominant stimulation occurs during the intestinal phase of digestion in response to chyme in the duodenum. Two major gastrointestinal hormones, secretin and cholecystokinin (CCK), released from the duodenum and the upper jejunal mucosa, play the central role in the control of exocrine pancreatic secretion. The primary stimulus is acid in the duodenum which causes the release of secretin, from enteroendocrine S cells located in the mucosa of the upper small intestine, into the blood stream. The secretin, carried by the blood to the pancreas, interacts with its specific G-protein-coupled receptor (GPCR) on the pancreatic ductal cells to stimulate the secretion of digestive juice and bicarbonate into the duodenum.

Stimuli such as long-chain fatty acids, peptides and amino acids in the duodenum cause the release of cholecystokinin from the duodenum and upper jejunal mucosa. Cholecystokinin stimulates the acinar cells of the exocrine pancreas to increase digestive enzyme secretion by activating the CCK receptors on the pancreatic acinar cells (Fig. 3).

CCK can also stimulate exocrine pancreatic secretion by neural pathways as well as hormonal pathways. CCK released into the blood stream in response to meal nutrients in the duodenum, can activate vagal afferent neurons that possess receptors for CCK, which carry the signal to the dorsal vagal complex where the sensory information is integrated, and eventually transmitted via the vagal efferent neurons to the exocrine pancreas to cause pancreatic enzyme secretion (Fig. 3). The neurotransmitters such as acetylcholine, gastrin-releasing peptide (GRP) and vasoactive intestinal polypeptide (VIP) released from the vagal efferent nerve endings stimulate the exocrine pancreatic enzyme secretion, through activation of G-protein-coupled receptors expressed on the pancreatic acinar cells.

Effects of physical exercise on exocrine pancreas

It has been reported that chronic swimming induced acceleration of meal-stimulated pancreatic secretion in...
From our studies, chronic compulsory endurance exercise by treadmill for 8 weeks increased pancreatic weight relative to body weight, pancreatic protein content, pancreatic enzyme activity, and basal amylase secretion in Wistar and Fischer rats. Since dietary composition and food consumption is known to influence pancreatic protein and enzyme content, food consumption was matched between the control and exercise groups. Thus, these augmentations of pancreatic protein content and enzyme secretion can be attributed to chronic exercise per se. In addition, in the study using electron microscopy, the morphology of the acinar cells was also observed to be affected by endurance exercise (Fig. 4). The acinar cells were markedly hypertrophied and the number of zymogen granules was increased in endurance exercise rats, suggesting that endurance exercise is capable of influencing the ultrastructure of the pancreatic acinar cells. Furthermore, there was no difference in the DNA content of the whole pancreas between the exercise and control groups, whereas the DNA content per gram of pancreatic tissue was significantly lower in the exercise group than in the control group. Thus, the increase of pancreatic weight induced by endurance running exercise training appears to be caused by hypertrophy of the acinar cells rather than proliferation of the acinar cells, which leads to an increase of pancreatic enzyme secretions.

We and another group have shown that voluntary wheel-running exercise training, as well as treadmill running exercise, increase the pancreatic weight, protein content, and enzyme activity of the pancreas. Also from our studies, electron micrographs (Fig. 4) revealed that acinar cells hypertrophied and zymogen granules increased in voluntary running groups. However, the total DNA content of the whole pancreas in the voluntary running group was significantly higher than the control group. These results suggest that voluntary wheel-running of low intensity exercise, performed long-term and daily, may cause augmentation of pancreatic enzyme synthesis and secretion through both hypertrophy and proliferation of the acinar cell.

Pancreatic enzyme secretion is well known to be regulated by gastrointestinal hormones such as CCK, which stimulates the acinar cells to increase digestive enzyme secretion either by directly activating the CCK receptors on the acinar cells or through acetylcholine released by the vagus nerve that possesses the CCK receptors. CCK also function as a proliferative hormone for pancreas and induces satiety by delaying gastric emptying.

To investigate the role of CCK in the effect of endurance exercise on exocrine pancreatic secretion, the pancreatic exocrine response to exogenous CCK-8 stimulation was examined. Intravenous injection of CCK-8 produced a significant increase in total pancreatic protein and amylase secretion in trained rats compared with the control rats, suggesting that endurance exercise can enhance the exocrine pancreatic secretion in response to CCK. Previous studies have demonstrated that acute exercise increases several serum gastrointestinal hormone levels. Also Ohta et al. showed that long-term chronic exercise increases the CCK content in the intestine. These studies suggest that CCK may play an important role in the enhancement of pancreatic enzyme secretion induced

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**Fig. 4** Electron micrographs of the pancreatic acinar cells in control (a), compulsory trained (b), voluntary trained (c) and CR-1505 treated plus compulsory trained rats (d). Note the acinar cells obviously hypertrophied and zymogen granules increased in compulsory (b) and voluntary (c) trained rats compared to the control rats (a). The bars indicate 2 μm.
Moreover, treatment with a CCK-A receptor antagonist, such as loxiglumide (CR1505), in treadmill trained rats inhibited the increase of pancreatic weight and hypertrophy of acinar cells induced by endurance training\(^{27}\). Further electron microscopic observations confirmed these results showing no morphological changes in acinar cells induced by endurance exercise under the treatment of a CCK-A receptor antagonist (Fig. 4). These results suggest that CCK plays a crucial role in mediating exercise-induced acceleration of exocrine pancreatic secretion. However, CR1505 administration showed a tendency to increase the pancreatic protein content and pancreatic enzyme activity in treadmill trained rats, suggesting the possibility that not only CCK but also other pathways may contribute to the exercise-induced enhancement of pancreatic secretion. Zsinka and Frenkl\(^{15}\) have demonstrated that regular swimming exercise increased the rate of pancreatic secretion and pancreatic enzyme activity, whereas this enhanced exocrine pancreatic function elicited by regular exercise was significantly reduced after vagotomy. Since chronic endurance exercise has been known to increase parasympathetic autonomic tone at rest\(^{28}\), the vagus nervous system also appears to play an important role in exercise-induced enhancement of the synthesis and storage of pancreatic enzymes.

Impairments of exocrine pancreatic function has been found in various physical conditions such as obesity\(^{29-32}\), diabetes\(^{33,34}\), and aging\(^{35,36}\). Changes in pancreatic enzyme activity and content have been reported in obese Zucker rats\(^{29-31}\) and in SHR/N-corpulent rats\(^{37}\). The obese Zucker rats, a well-studied genetic model of obesity\(^{38,39}\), exhibited profound obesity, hyperlipidemia, hyperinsulinemia and insulin resistance\(^{40}\). From our studies, the obese rats became overweight and exhibited elevated levels of serum total cholesterol and triglycerides; whereas the pancreatic weight, pancreatic protein contents and amylase activities markedly decreased in obese Zucker rats fed ad libitum compared with that in lean rats, indicating decreased exocrine pancreatic function induced by obesity\(^{41}\). Furthermore, electron microscopic observation of the exocrine pancreas from obese rats revealed atrophy of the acinar cells, a decrease in the number of zymogen granules and accumulation of lipid droplets when compared with lean rats (Fig. 5a). These ultrastructural alterations show the effect of severe obesity both on the ultrastructure and function of the exocrine pancreas. Voluntary wheel-running exercise training combined with an energy-restricted diet attenuated weight gain and reduced serum lipids in exercised rats compared to obese rats. In addition, the effects of exercise training on genetically obese rats, involved in amelioration of exocrine pancreatic function that increased pancreatic weight, protein content, and enzyme activity, and also induced the ultrastructural abnormalities of acinar cells to restore toward the normal structure (Fig. 5b).

**Conclusion**

It appears that any type of endurance exercise training, such as swimming or running, or either voluntary or compulsory, may accelerate exocrine pancreatic secretion. Particularly, a low-intensity exercise, like voluntary wheel-running performed daily over a long-term, which may be equivalent to a high level of daily physical activity, appears to be sufficient to cause augmentation of pancreatic enzyme synthesis and secretion through both hypertrophy and proliferation of acinar cells. Further, beneficial effects induced by chronic endurance exercise could be expected, not only in normal rats, but also in

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**Fig. 5** Electron micrographs of the pancreatic acinar cells from obese (a) and trained (b) rats. Note numerous lipid droplets (arrows) with dilated rough endoplasmic reticulum in obese (a) rats. The bars indicate 1 μm.
obese rats to reduce abnormalities at the ultrastructural levels as well as exocrine pancreatic functional levels. Considering that the exocrine pancreas is the major source of enzymes responsible for food digestion, its beneficial adaptation to exercise plays an important role in endurance exercise performance, which requires a large energy supply from food.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this article.

Acknowledgments

This review work was partially supported by JSPS KAKENHI Grant Number (10680071) (1998–2001) and a research grant from Mizuno Sports Promotion Foundation (2005) in JAPAN.

References


