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ABOUT COVER

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EDITORIAL

Editorial on amylase and the acini–islet–acinar reflex: A new frontier in metabolic health research

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Abstract

This editorial comments on the study by Pierzynowska *et al* investigating the acini-islet-acinar (AIA) reflex, which integrates the exocrine and endocrine functions of the pancreas. The study investigates whether exogenous amylase introduced to the interstitial fluid surrounding pancreatic islets can inhibit insulin release. Historically, high serum amylase levels were associated with pancreatitis, but recent findings suggest that low amylase levels are more linked to metabolic diseases like diabetes and obesity. In their experiment, six pigs were used to examine the effects of amylase infusion on insulin release during an intravenous glucose tolerance test. The pigs received different treatments (amylase, saline, or bovine serum albumin), and blood samples were taken over two hours to measure insulin and glucose levels. The results showed amylase delayed glucose-stimulated insulin release, whereas bovine serum albumin increased insulin levels supporting the existence of the AIA reflex and suggesting amylase as a key metabolic regulator. Enzyme supplementation, particularly with α-amylases, may offer therapeutic benefits in preventing and managing metabolic disorders, including diabetes and obesity. Further research is warranted to explore the full scope of amylase's role in metabolic health and its therapeutic potential.

Key Words: Alpha-Amylase; Insulin secretion; Glucose metabolism; Pancreatic signaling; Metabolic regulation; Acino-insular axis

Core Tip: This editorial emphasizes the critical role of α-amylase, an enzyme essential for starch digestion, in metabolic regulation beyond its digestive function. Recent studies, including that of Pierzynowska *et al*, demonstrate that amylase can inhibit insulin secretion, delaying glucose clearance and increasing blood sugar levels, with effects persisting even after the infusion. This suggests amylase's influence on pancreatic signaling and confirms the existence of the acini-islet-acinar reflex. Understanding the broader metabolic role of amylase may open therapeutic avenues for conditions like diabetes and obesity through enzyme supplementation, highlighting the need for further research into its regulatory mechanisms.

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INTRODUCTION

The exocrine pancreas, with acinar cells comprising 85%-90% of its mass, produces essential digestive enzymes, primarily amylase (a glycolytic enzyme) and lipase (a lipolytic enzyme). These acinar cells are located near the endocrine islets of Langerhans, which secrete insulin, a hormone crucial for regulating blood glucose and overall metabolic health. An insulin deficiency is associated with pancreatic atrophy and exocrine pancreatic insufficiency, highlighting the interconnected roles of the exocrine and endocrine pancreas[1]. Historically, pancreatic endocrine and exocrine functions have been viewed as distinct; however, recent studies reveal a coordinated relationship between these functions, challenging the traditional view of their independence.

The study by Pierzynowska *et al*[2], published in the *World Journal of Experimental Medicine*, provides new insights with the proposed acini-islet-acinar (AIA) reflex, which connects pancreatic acinar cells to insulin-producing islet cells[2]. This reflex suggests that α-amylase may influence insulin secretion by altering pancreatic interstitial fluid dynamics, linking exocrine activity to endocrine response. Pigs were chosen as suitable models for studying insulin secretion and pancreatic enzyme dynamics due to anatomical and physiological similarities between their pancreas and that of humans, compared to rodents.

After a stabilization period, pigs underwent an intravenous glucose tolerance test with a glucose bolus injected into the jugular vein while simultaneously amylase solution was infused into the pancreatic artery in select pigs. This setup was designed to evaluate the hypothesized AIA reflex by examining how increased amylase in the pancreatic interstitial fluid affects insulin release. Blood samples were then collected at specific intervals to assess glucose and insulin levels over time, tracking the physiological response to glucose. Findings on the AIA reflex thus reveal a more complex interaction between the endocrine and exocrine pancreas, with implications for understanding glucose and lipid metabolism mechanisms, particularly concerning metabolic diseases such as type 2 diabetes and obesity. This study, by exploring the integrative endocrine (hormonal) and exocrine (digestive) roles of the pancreas, aims to advance our understanding of metabolic health, with the potential to enhance future diagnostics and treatments for metabolic diseases.

AMYLASE AND INSULIN RELEASE

α-Amylase is an enzyme that catalyzes the hydrolysis of internal α-1,4-glycosidic linkages in starch, breaking it down into glucose, maltose, and maltotriose. This process begins in the mouth, where salivary α-amylase initiates carbohydrate digestion. The feedback mechanism between amylase activity (carbohydrate digestion) and insulin release (glucose regulation) plays a crucial role in maintaining blood sugar balance. As amylase converts carbohydrates into glucose, rising blood glucose levels prompt insulin release to facilitate glucose uptake and storage, preventing significant fluctuations in blood sugar that could lead to hyperglycemia or hypoglycemia[3].

The AIA axis reflex integrates this feedback mechanism at the pancreatic level, linking acinar cells, which release digestive enzymes, with the islet cells, which release insulin. This cross-talk is vital for efficiently meeting metabolic demands. In cases of insulin resistance or diabetes, this feedback loop is disrupted, as impaired insulin release or action interferes with normal blood glucose management. Even as amylase continues carbohydrate breakdown, elevated glucose levels persist in the bloodstream due to insufficient insulin response, emphasizing the importance of balanced amylase activity and insulin response for metabolic health.

Interestingly, studies show a negative correlation between serum amylase levels and fasting blood glucose in diabetic populations (Table 1), with lower amylase levels associated with greater glucose dysregulation[1,4-6]. This supports the findings that individuals with higher salivary amylase activity often have lower postprandial glucose levels and better starch adaptation, suggesting that enzyme levels in the AIA axis might play a role in metabolic resilience and glucose homeostasis.

Recent research suggest that low amylase secretion may underlie blood sugar abnormalities[7,8]. Enzymatic supplementation with α-amylases could help prevent and treat these undesired physiological disorders. Purified combinations of pancreatic proenzymes/enzymes such as trypsinogen/trypsin, chymotrypsinogen/chymotrypsin, and amylase[9] have been shown to have strong antimetastatic and anticancer properties. Such proenzyme/enzyme combinations have

Table 1 Serum amylase levels and metabolic indicators in different health states[4-6]

Metabolic states/groups	Healthy	Pre-diabetic	Diabetic	Ref.
Amylase levels (IU/L)	25-125	40-80	30-60	Yadav *et al*[4]; Khan *et al*[5]
Fasting blood glucose (mg/dL)	70-99	100-125	126 and above	Khan *et al*[5]; American Diabetes Association Professional Practice Committee [6]
HbA1c (%)	< 5.7	5.7-6.4	6.5 and above	American Diabetes Association Professional Practice Committee[6]
Total cholesterol (mg/dL)	Below 200	180-200	200 and above	Yadav *et al*[4]; Khan *et al*[5]
Triglycerides (mg/dL)	100-150	150-200	200 and above	Yadav *et al*[4]; Khan *et al*[5]

HbA1c: Glycated hemoglobin.

been implicated in inhibiting tumor cell migration at the cellular level. These findings point to the potential health benefits of enzyme supplements and warrant ongoing research and clinical trials.

DISCUSSION

The modulation of pancreatic function is complex, involving neurological and hormonal signals. Acinar cells produce pancreatic enzymes, and insulin regulates exocrine secretion through the AIA reflex. Notably, a fast intravenous glucose infusion in one study significantly reduced amylase secretion, indicating a close interaction between glucose levels and enzyme release[10].

The AIA model posits that pancreatic acini and islets coordinate through biochemical signaling to maintain a balance between digestion and metabolism in response to food intake[11]. This interaction is mediated through paracrine and neuroendocrine pathways, enabling mutual regulation between acinar cells' amylase secretion and beta cells' insulin release[12].

Pierzynowska *et al*'s experiment on pigs investigated the possibility of an AIA reflex, specifically examining the reciprocal amylase and insulin interactions, to confirm both the presence of the reflex and the close anatomical integration of exocrine and endocrine pancreatic components[2]. The study found that exogenous amylase infusion into the pancreas delayed glucose-stimulated insulin secretion, suggesting a functional link between acinar enzyme activity and islet function. Pigs with compromised exocrine function showed delayed insulin responses, and enzyme supplementation improved glucose clearance. These findings imply that pancreatic enzymes might influence blood glucose utilization independently of insulin release[13].

Previous research indicates that amylase may limit insulin secretion by redirecting glucose from the bloodstream to the intestine[14]. In general, gut amylase reduces glucose absorption and insulin release. This shift in glucose utilization, potentially mediated by enterocytes before glucose reaches the bloodstream, could represent an insulin-independent glucose regulation mechanism[10].

In Pierzynowska *et al*'s study, insulin levels remained unexpectedly low under glucose loading, with glucose peaking at 400 mg/dL within 15 minutes[2]. Remarkably, amylase's suppressive effect on insulin secretion persisted for 30 minutes post-infusion, possibly due to altered pancreatic interstitial signaling or slowed beta-cell recovery. In insulin-resistant conditions, AIA reflex feedback may be impaired, allowing glucose to accumulate in the bloodstream, potentially exacerbating hyperglycemia. This chronic hyperglycemia may further strain beta cells, disrupting their role in modulating acinar cell responses during digestion. These insights also point to a complex regulatory network influenced by other metabolic pathways.

Emerging evidence suggests that changes in amylase levels, either due to exogenous or endogenous factors, may affect the gut microbiome, which, in turn, could influence pancreatic insulin release. High amylase levels may deplete beneficial short-chain fatty acid-producing bacteria, disrupting insulin signaling and delaying glucose-stimulated insulin release[7]. Increasing evidence also highlights the microbiome's influence on the development of metabolic disorders, underlined by correlations between the salivary and urinary metabolome and pediatric obesity[14].

Removing pancreatic enzymes from pigs' digestive systems significantly reduced glucose absorption after oral glucose loading, supporting the idea that active salivary amylase in the alimentary canal enhances glucose uptake. Low serum amylase levels are associated with a higher risk of metabolic syndrome, and there is a noted negative correlation between salivary amylase levels and obesity. Genetic studies reveal individuals with high amylase gene copy numbers produce more salivary amylase, which can increase glucose absorption and potentially predispose them to fat accumulation. Interestingly, however, high amylase gene copies have also been linked to a lower risk of obesity, suggesting an inconclusive, gene-dependent relationship with metabolic health[15].

FUTURE DIRECTIONS AND RECOMMENDATIONS

Hyperglycemia has been associated with several pathological conditions like diabetes and obesity. Adequate insulin signaling is essential to counteract these effects. The inhibition of insulin signaling by amylase presents a critical research question that demands an urgent answer to combat metabolic diseases. Further studies are needed to completely understand how amylase affects the broader metabolic network and pancreatic function, possibly *via* gut microbiome interactions. This could provide better insights into the regulation of insulin secretion and its consequences for metabolic health.

Recent developments, including advanced three dimensional imaging of pancreatic innervation, have provided deeper insight into the AIA reflex's anatomy and function. This imaging has demonstrated the intricate innervation pathways that link acinar and islet cells, highlighting their integrated roles in metabolic health and revealing the dysregulated neural signaling often found in metabolic diseases[16]. Additionally, therapies targeting the AIA reflex offer therapeutic strategies for managing blood glucose levels, with α-amylase as a potential modulator. Understanding and potentially manipulating the AIA reflex represents a promising frontier for treating metabolic diseases.

CONCLUSION

The study by Pierzynowska *et al*[2] sheds new light on the integrative functions of the pancreas through the AIA reflex, emphasizing the significant role of amylase in metabolic regulation. The findings suggest that targeted enzyme supplementation could be a promising strategy to enhance metabolic health and mitigate conditions like diabetes and obesity. Beyond digestion, amylase emerges as a potential metabolic biomarker, with reduced levels indicating early dysfunction. By exploring the AIA reflex further, we may advance our understanding of enzyme-based therapeutic interventions, providing novel approaches for early diagnosis and effective management of metabolic diseases.

FOOTNOTES

Author contributions: Deji-Oloruntoba O, Okpete UE and Byeon H contributed to this paper; Byeon H designed the study; Deji-Oloruntoba O, Okpete UE involved in data interpretation and developed methodology; Deji-Oloruntoba O, Okpete UE and Byeon H assisted with writing the article.

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