Review: The Ageing Pancreas

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Abbreviations and Acronyms

GSIS – Glucose-stimulated insulin secretion **/Year><RecNum>418</RecNum><DisplaNAD -** **NAD - Nicotinamide adenine dinucleotide** **NEFA – Non esterified fatty acid**	**PDX-1 - Pancreatic and duodenal homeobox 1** **SIRT1 – sirtuin 1** **UCP2 – Uncoupling protein 2**

Abstract

Type 2 diabetes is historically associated with older adults, and glucose tolerance is known to decline with advancing age. During the course of natural ageing, changes in many peripheral tissues contribute to this deterioration of glucose homeostasis. Included in this process are changes to the structure and function of the pancreatic islets, which undergo deviation in endocrine responses to glycaemic challenge. Current knowledge about the changes seen in the ageing pancreas is reviewed here.

Introduction

In the coming decades both developed and developing societies face a dual crisis of an increasingly ageing population and an increased prevalence of obesity and diabetes. It is commonly accepted that the UK population is becoming increasingly skewed towards older adults, (1), and alongside this, increases in obesity (1) and type 2 diabetes (2) represent significant health, social and economic pressures in the short to mid-term. This provides a unique challenge for scientists, physicians and policy makers.

The ageing process negatively affects the majority of tissues of the human body, including those associated with the onset of diabetes. It is now well established that the incidence of type 2 diabetes increases with age (3, 4) but specific reasons for this are as yet unclear. Diabetes significantly lowers the chances of successful aging, and notably increases functional limitations and impairs quality of life (5). Contemporary scientific opinion would suggest that this is most likely due to the gradual increase in insulin resistance seen in peripheral tissues as we age (6, 7). This phenomenon is therefore likely to increase due to the increasing prevalence of obesity and sedentary lifestyles (8, 9). Interestingly, however, key age-related changes in peripheral body composition, notably increased adiposity and decreased skeletal muscle mass, that are associated with insulin resistance

have been shown to be insufficient on their own to account for the changes in glucose tolerance associated with type 2 diabetes (10).

One factor often overlooked when considering the close association between ageing and type 2 diabetes prevalence is the pancreas, and its ability to consistently maintain an appropriate endocrine output .

Pancreatic islets and ageing: insulin secretion

A primary role of the pancreatic islet is to synthesise, store and release insulin from the β-cells when required (11). β-cells make up approximately 55% of the cellular mass of a pancreatic islet (around 75% in rodents) and α-cells 35% (17% in rodents) (12). Figure 1 demonstrates diagrammatically the makeup of a human pancreatic islet. To successfully manage blood glucose levels, both pancreatic β-cell function and mass must be maintained, and both of these factors are known to be influenced by the ageing process.

The first of these essential factors influenced by age, insulin secretion, has been the focus of a significant amount of research over the previous two decades. Although initial studies provided conflicting data (13) it is now accepted that after a long period of normal, or even elevated insulin levels (particularly in obese individuals) insulin secretion falls with advancing age (14, 15), and this is independent of insulin action in peripheral tissues (16) While increased demands for more insulin are incurred by insulin resistance, several studies suggest that age-related decreases in insulin secretion are not due solely to the increased glycaemic pressure placed on pancreatic islets in a progressively insulin resistant environment, but that independent age-related factors are somehow involved. These 'insulin resistance-independent factors' are thought to include loss of expression of pancreatic β-adrenergic receptors (17), which would impinge upon adrenergic stimulation of insulin secretion. A dysregulation of sirtuin activity by pancreatic β-cells has been reported (18, 19), which might lead to changes in UCP2 activity leading to suppressed insulin secretion. Reduced circulating levels of the insulin secretion regulating vitamin D have also been associated with age-related changes in insulin secretion (20) as well as dysregulated expression of the orphan GPR39 receptor (21). Further research has suggested that altered incretin levels (22) and NAD biosynthesis (23) might play a role in both secretion and biosynthesis of insulin in older animals (see Table 1). The incretin GIP appears to produce a 48% lower insulin secretion response with age (24) suggesting that incretin sensitivity may be impaired in older adults.

The reduction in insulin secretion seen in ageing has also been suggested to be due to decreased biosynthesis (25) and reduced stimulus-recognition-secretion-coupling (26, 27). As the islet releases many other molecules in addition to insulin, some of which can regulate insulin release, the possibility exists that changes in these molecules might be involved in age-related decline in insulin secretion. An example of this would be IAPP, which is co-secreted with insulin and which can aggregate within pancreatic islets and impair insulin release (28)

Factor	Role	Effect in ageing pancreas	Reference
Chromosomal Telomere	Protective chromosomal structure	Decreased insulin secretion, increased senescence	59
GPR39	Unknown	Decreased insulin secretion	20
IAPP	Slows gastric emptying	Increased β-cell apoptosis	28
Incretins (GLP-1, GIP)	Modulators of post-prandial islet response	Decreased insulin secretion and β-cell mass	24
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NAD	Metabolic coenzyme	Decreased insulin secretion	23
$p16^{INK4a}$	Cell cycle regulator	Limited β-cell regeneration	47
P2 receptor	Cell surface nucleotide receptor	Decreased insulin secretion	48
PDX-1	Transcription factor	Decreased insulin transcription, increased β-cell apoptosis	45, 50
Sirt1	Epigenetic gene regulator	Represses UCP2 leading to decreased insulin secretion	18, 19
Vitamin D	Fat soluble vitamin	Decreased insulin secretion and sensitivity	20

Table 1. Factors associated with age-related decline in pancreatic function. Changes in the expression levels and activities of the molecules listed in this table have been associated with alterations in pancreatic islet function seen in older organisms.

Whatever the mechanism, it is clear that pancreatic β-cell function appears to decrease as glucose levels increase, even within the normal range (29) and that the insulin secretory capacity of the pancreas decreases with age (30-32). It has been suggested that insulin secretion decreases by 0.5% per year of life (33, 34) and that in people with type 2 diabetes a significant decrease occurs in the first few years post-diagnosis (35). Therefore, ageing has a significant effect on the first of our essential pancreatic factors, insulin secretion. Compounding this effect is the observation that increased hepatic clearance of insulin occurs, dampening the delivery of insulin to peripheral tissues (36).

Pancreatic islets and ageing: pancreatic β-cell mass

Alongside pancreatic β-cell function, maintenance of effective pancreatic β-cell mass is essential in enabling the body to control blood glucose levels. Changes in the pancreatic islet seen in ageing are likely to be due to loss of β-cell mass, with little evidence of changes in the numbers or topographical location of other cell types, apart from in those who have diabetes where an expansion of α-cells is seen (37). β-cell mass is under normal circumstances maintained by a relatively labile combination of β-cell neogenesis and apoptosis (38). A significant divergence in the levels of either of these two factors may therefore lead to a decrease in the total number of pancreatic β-cells, and a subsequent inability of the pancreas to respond to elevated blood glucose with an appropriate insulin secretory response. Much recent research has focussed upon the role of incretins (and their analogues) in the maintenance of β-cell mass, as a wealth of evidence of their role in this area (39-41) has led to the notion of incretin-based therapies being used not only to manage blood glucose levels, but also to support pancreatic β-cell mass (42). Additionally, research has suggested that cell-cell interactions within the islet are essential for insulin production, with connexins playing an important role (43).

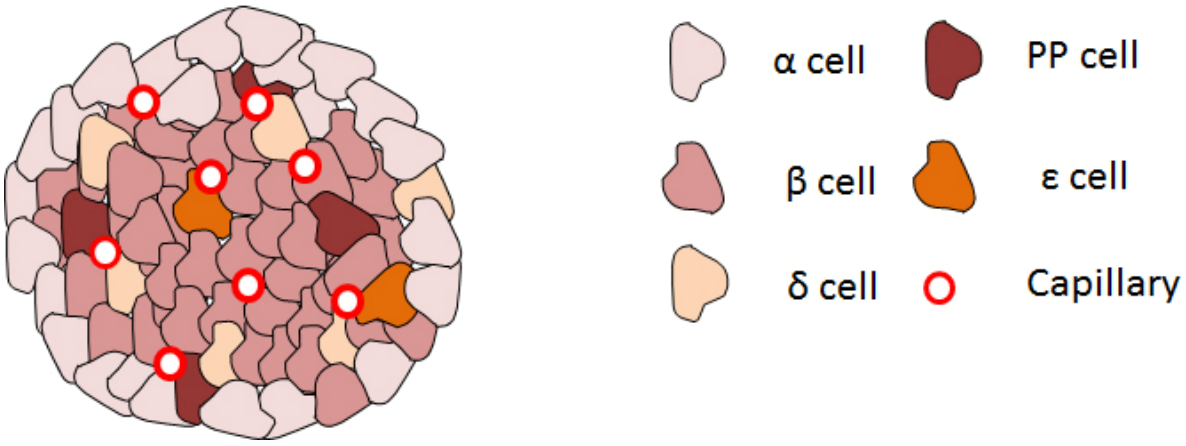

Figure 1. Diagrammatic representation of a pancreatic islet. Changes observed in pancreatic islets as they undergo ageing are thought to be due to a decreased number of β-cells with little evidence of changes seen in other cell types.

There is strong evidence in both rodents and humans that the ageing process leads to a reduced capacity for β-cell neogenesis or proliferation (44, 45). Equally, research has identified an age-related increase in sensitivity to apoptosis (45) in pancreatic β-cells and increased age-related β-cell apoptosis in the presence of obesity (46). As the level of cellular turnover in pancreatic islets is relatively slow, and appears to be limited to the first three decades of life (47), the ability of the pancreas to respond to apoptotic pressures exerted on it is significantly impaired .The mechanisms for increased apoptosis in ageing β-cells are thought to include accumulation of the tumour suppressor $p16^{INK4a}$ (48) and P2 receptor expression (49). In addition, it has been postulated that age-related changes in β-cell turnover (a result of both neogenesis and apoptosis) are due to

reduced expression of the transcription factor PDX-1 (45, 50), an essential element in not only the transcription of insulin, but also a potent inhibitor of β-cell apoptosis (51, 52).

The role of diabetes in pancreatic ageing

The endocrine pancreas of a subject with type 2 diabetes clearly has a more challenging environment in which to age than that of a lean, healthy individual. The chronically elevated levels of both glucose and non-esterified saturated fatty acids that are a common occurrence in type 2 diabetes are known to reduce GSIS after chronic exposure, a phenomenon termed glucolipotoxicity (53, 54). Alongside the decrease in GSIS, elevated glucose and NEFAs are known to induce β-cell apoptosis and therefore compound their effects on insulin secretion (55). Interestingly, recent research has suggested that glucolipotoxicity impairs β-cell function in an age-dependent manner (56), causing diminished GSIS, proinsulin biosynthesis, lower cellular insulin content and reduced expression of β-cell gene expression. Suggested mechanisms for this toxicity include increased reactive oxygen species and decreased mitochondrial function (57), phenomena that have been shown to accumulate as islets age (58).

In addition to these well documented challenges, it has been reported that individuals with type 2 diabetes have accelerated shortening of telomeres, the regions of DNA repeats found at the end of chromosomes (59), leads to compromised β-cell survival (60) suggesting that the process of ageing itself can have a significant impact on the regenerative capacity of the endocrine pancreas.

Conclusion

As the human body ages, and especially as glycaemic pressures increase due to obesity or insulin resistance, our pancreatic islets change in morphology and function. Not only does the number of pancreatic β-cells decrease as the balance of new cell growth and apoptosis shifts, but the transcriptome and proteome of the islet changes to contribute to a tissue that is no longer fully able to perform its primary function and contributes to the increased incidence of diabetes seen in elderly populations.

Key messages

Insulin secretion decreases 0.5% per year

β-cell neogenesis and proliferation decrease with age

Ageing impairs ability of islet cells to perform their primary functions

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