Effects of Ageing on Insulin Secretion and Action

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Key Words

Insulin · Insulin resistance · Ageing · Type 2 diabetes mellitus · Insulin secretion

Abstract

One of the many conditions associated with ageing is type 2 diabetes mellitus, the prevalence of which increases from 20–30 years of age onwards. In many cases, type 2 diabetes mellitus is caused by the combination of insulin resistance and poor insulin secretion. Insulin resistance is also a risk factor associated with other disorders, in particular cardiovascular disease. Physiological changes associated with ageing, such as changes in body composition, decreased physical fitness, changes in hormones, and the secondary effects of high levels of free fatty acids and glucose, may also contribute to the impairment of insulin secretion and action. In this review, the effects of ageing on the secretion and action of insulin will be highlighted.

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Introduction

Propelled by the ever-growing world population and the continual rise in life expectancy, ageing is becoming a more frequent and lengthy 'condition'. The process of

ageing is characterized by a number of physiological and pathophysiological alterations, which, in many cases, can lead to impaired physical performance and increased morbidity and mortality. Type 2 diabetes mellitus (non-insulin dependent) is such an example. Data from the Framingham Study show unequivocally that the incidence of type 2 diabetes rises steeply with age, at an almost exponential rate, from the age of 20–30 years onwards [1]. Prevalence rates show a similar pattern from 1% between 30 and 40 years of age to more than 15% above 80 years of age. These observations were published in 1986 and both the incidence and prevalence rates are continuously rising because of increased life expectancy, increased prevalence and magnitude of obesity, and poor inclination to physical activity. The picture becomes even more alarming when one considers pre-diabetic states. Type 2 diabetes is, in most cases, caused by a combination of defective insulin secretion and insulin resistance. At present, there is accumulating evidence that insulin resistance is a substantial risk factor for cardiovascular disease [2, 3]. The terms 'metabolic syndrome', 'insulin resistance syndrome', 'syndrome X', 'dysmetabolic syndrome' and others have been proposed to represent the clustering of insulin resistance, obesity, hypertension, dyslipidaemia and hypercoagulability. According to World Health Organization criteria, the metabolic syndrome is defined as the coexistence of insulin resistance and two out of the following four conditions: (1) obesity, (2) dyslipidaemia,

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(3) microalbuminuria, and (4) hypertension [4]. Thus, a substantial proportion of the co-morbidity and co-mortality that occur with diabetes and the metabolic syndrome – in particular, cardiovascular disease – may directly or indirectly relate to the changes in insulin secretion and action that evolve with ageing. In this brief review, some of the changes in insulin action and secretion that occur in the process of ageing will be briefly outlined.

Insulin Secretion

Insulin secretion is pulsatile with rapid, low amplitude pulses every 8–15 min and ultradian pulses with larger amplitude at a periodicity of 60–140 min [5, 6]. The majority of the secretory mass is accounted for by pulses, whereas interpulse secretory activity is modest [5]. The physiological pulse secretory pattern is disrupted in a number of pathological conditions such as impaired glucose tolerance, obesity and type 2 diabetes [5, 6].

Ageing is characterized by a progressive loss of β -cell function. In a study involving 957 participants, it was reported that post-hepatic insulin delivery dropped by 25% between the ages of 18 and 85 years [7]. Furthermore, ageing is associated with gross impairment of glucose-stimulated insulin pulse mass, amplitude and rhythmicity [6]. Deterioration of β -cell function with advancing age may, undoubtedly, contribute to the increased incidence and prevalence of type 2 diabetes, although the underlying mechanism remains, to a large extent, uncertain.

Insulin Action

Insulin resistance may be defined as subnormal biological responses to insulin exposure and may be observed at the cellular level, in intact tissues or at the whole body level [8]. Most often, the term insulin resistance is used to signify resistance to the actions of insulin on glucose metabolism, i.e. an inadequate suppression of endogenous glucose production in liver and kidney, and an inadequate stimulation of glucose disposal in striated muscle and other insulin-sensitive tissues. The ‘gold standard’ technique for measuring insulin resistance in humans is the hyperinsulinaemic glucose clamp; this technique involves a fixed dose of insulin being administered and then normal glucose concentrations being maintained by the infusion of glucose – the amount of glucose given (the glucose infusion rate or ‘M-value’) reflects insulin sensitivity

and is an inverse measure of insulin resistance [9]. Other parameters, such as fasting insulin levels, may also be used.

A number of studies have shown that ageing is accompanied by insulin resistance. Euglycaemic clamp studies consistently demonstrate that elderly individuals are insulin resistant and that the dose-response curve for insulin is shifted to the right [10, 11]. There is evidence that the reduction in insulin sensitivity that occurs with ageing involves both impairment of the suppression of endogenous glucose production and of peripheral glucose utilization [12]. It is again evident that deterioration of insulin sensitivity with increasing age contributes to the increased occurrence of type 2 diabetes.

Mechanisms Contributing to Altered Insulin Secretion and Action

Many physiological alterations occurring with ageing may contribute to the impairment of insulin secretion and insulin action, including altered body composition, decreased physical fitness, changes in other hormones (e.g. growth hormone, insulin-like growth factors, sex steroids, leptin), and lipotoxicity and glucose toxicity secondary to sustained elevations of circulating free fatty acids and glucose. Despite vigorous individual attempts to avert the physical impact of age, virtually all population-based studies show a relentless decrease of lean body and muscle mass and an increase of fat mass [13–16]. The decline in muscle mass may to a large extent be explained by a decrease in the fractional synthetic rate for muscle proteins [13, 16]. In addition, there is evidence that there is a progressive loss of muscle quality (i.e. muscle function/muscle mass) [16]. The combination of loss of muscle mass and increased muscle weakness and fatigability, resulting in substantial impairment of muscle function, has been coined ‘sarcopenia of ageing’. In relation to insulin action, these processes are important, because decreased muscle mass and increased fat mass lead to insulin resistance [15]. Supporting this idea, Ferranninni and colleagues reported that the age-related changes in insulin sensitivity were no longer apparent after correction for body mass index [17]. Physical fitness and aerobic capacity (VO_2 max) also decline with ageing, which may contribute to the impairment of insulin sensitivity [16, 18].

The secretory patterns and actions of many hormones also change with age. Leptin, for instance, is released from adipocytes and acts on the central nervous system to decrease appetite. In general, there is a very clear positive

relationship between leptin and fat mass. In elderly individuals, however, this correlation is disrupted [19], suggesting an impairment of the feedback between peripheral fat stores and appetite regulation, which may contribute to the increased prevalence of obesity with age.

Many of the aberrations mentioned above may be sustained and amplified by glucose and lipotoxicity [20–23]. There is a large body of experimental evidence to show that prolonged elevations of glucose and free fatty acids impair β -cell function and induce insulin resistance. To what extent ageing itself contributes to the deterioration of insulin secretion and insulin action observed in the elderly remains uncertain.

Conclusion

In conclusion, it is beyond doubt that ageing is associated with a relentlessly progressive impairment of both insulin secretion and action. Whether this deterioration is intrinsic to ageing or secondary to changes in body composition or secretion or action of other hormones – and if so in principle could be modified therapeutically – remains to be settled.

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