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Review Article

The Interaction between Metabolic Disease and Ageing

Abstract

Two of the greatest crises that civilisation faces in the 21st century are the predicted rapid increases in the ageing population and levels of metabolic disorders such as obesity and type 2 diabetes. A growing amount of evidence now supports the notion that energy balance is a key determinant not only in metabolism but also in the process of cellular ageing. Much of genetic evidence for a metabolic activity-driven ageing process has come from model organisms such as worms and flies where inactivation of the insulin receptor signalling cascade prolongs lifespan. At its most simplistic, this poses a conundrum for ageing in humans – can reduced insulin receptor signalling really promote lifespan and does this relate to insulin resistance seen in ageing? In higher animals, caloric restriction studies have confirmed a longer lifespan when daily calorie intake is reduced to 60% of normal energy requirement. This suggests that for humans, it is energy excess which is a likely driver of metabolic ageing. Interventions that interfere with the metabolic fate of nutrients offer a potentially important target for delaying biological ageing.

Introduction

In the coming decades the UK faces a dual crisis of an ageing population and increasing levels of obesity and associated disorders, including diabetes. Demographic research has confirmed that the UK and European populations are increasingly skewed towards older adults [1], and that this trend is likely to continue in the future. Added to this, concomitant increases in obesity [2] and type 2 diabetes [3] represent significant social, medical and economic challenges in the future.

The process of ageing negatively affects many tissues in the human body, e.g. decreasing collagen elasticity and increasing collagen deposition in fibrosis, but ageing has a particularly significant impact on those tissues associated with nutrient metabolism such as the pancreas. It is well established that the incidence of the metabolic disorder type 2 diabetes, a disease that is characterised by elevated blood glucose levels, increases with age [4,5]. This may be due to the fact that as the human body ages, peripheral tissues become less sensitive to the actions of the hormone insulin, secreted from the pancreas in response to post-prandial increases in blood glucose [6]. The specific reasons for this age-related decrease in insulin sensitivity are not fully understood, and may reflect a failure to adapt to chronic metabolic stress. Diabetes itself is known to significantly decrease the chances of successful ageing, and notably increases the extent of functional impairment in vision, renal function and cognitive function [7].

Increasing evidence suggests that energy balance is central to both successful ageing and protection from metabolic disorders. The close links between these two phenomena are reviewed here.

Ageing and energy balance: restriction of nutrients

The recent proliferation of research into ageing and longevity across multiple cells/organisms has produced some fascinating candidate regulatory molecules and pathways. From extensive research using *Caenorhabditis elegans* and rodent models, we can now manipulate genes associated with several key signalling pathways that play significant roles in the ageing process. It is fascinating that a large proportion of these pathways are also involved in energy balance and metabolic disorders (an example of the complex interplay of these pathways is illustrated in Figure 1).

At one extreme of this relationship is the well-established field of caloric restriction (CR). It has been known for some 70 years now [8] that a link exists between CR and longevity. CR is currently the only dietary intervention that is proven to increase longevity and delay the onset of age-related decline [9] and has been demonstrated in a wide variety of organisms, including *Caenorhabditis elegans* [10,11], *Saccharomyces cerevisiae* [12,13], *Drosophila melanogaster* [14], rodents [15,16], but in primates CR appears to not affect longevity, but clearly delay age-associated disorders improving health [17-19,20].

Research into the mechanisms behind the CR-longevity link has repeatedly pointed to either hormetic or metabolic genes/proteins as being of key importance. The best characterised of these are the sirtuins (SIRT), mammalian homologues of the yeast NAD^+-dependent deacetylase sir2 [21]. SIRT1, in particular has been shown to regulate CR induced increases in longevity in many organisms [22], although SIRT1 independent pathways have also been identified [23,24]. Upon closer inspection of the mechanism of action of CR-induced SIRT1 activity, the link between ageing and metabolism first becomes clear.

SIRT1 catalyses the de-acetylation of a number of targets associated with metabolism and energy homeostasis upon activation by CR, and this process leads to transcriptional regulation of several

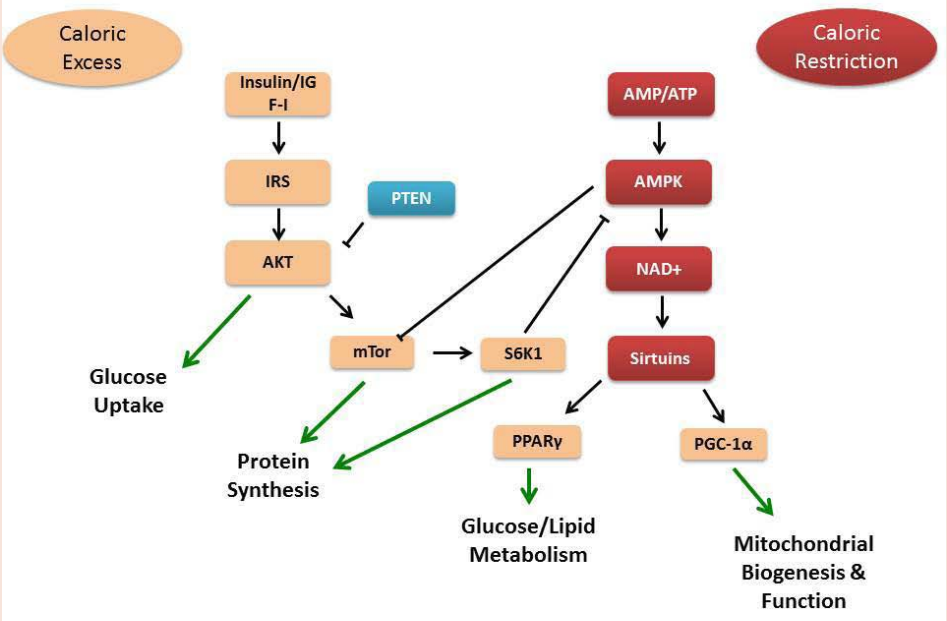

Figure 1: Signalling pathways associated with caloric excess and caloric restriction. The interaction between the signalling molecules associated with longevity and their activation or inhibition by exposure to either excess or insufficient calories demonstrates the close links between metabolism and ageing. Key: AMP = adenosine monophosphate; ATP = Adenosine triphosphate IGF = insulin-like growth factor; IRS = insulin receptor substrate; AKT = protein kinase B; mTor = mammalian target of rapamycin; NAD = nicotinamide adenine dinucleotide; PGC-1α = Peroxisome proliferator-activated receptor gamma coactivator 1-alpha; s6K1 = ribosomal protein S6 kinase beta-1; PPAR = peroxisome proliferator-activated receptor.

key metabolic factors such as protein tyrosine phosphatase 1B (PTP1B), a negative regulator of insulin signalling, IRS1 and liver X receptor (LXR). CR-induced activation of SIRT1 causes a de-acetylation of LXR which, alongside down-regulation of PTP1B, ultimately results in decreased insulin resistance [25]. To accompany this decrease in insulin resistance, SIRT1 activation also causes an increase in insulin secretion from pancreatic β-cells [26]. Therefore, while SIRT1 is essential for maintaining glucose sensitivity it shows decreased expression in aged versus young tissues. The SIRT1-dependent improvements in insulin homeostasis, coupled with increases in hepatic glucose output mediated by de-acetylation of the transcription co-activator peroxisome proliferator-activated receptor-γ (PPARγ) co-activator 1α (PGC1α) [27], which also induces a high efficient mitochondria biogenesis [28], indicate how pivotal energy balance and metabolism are to hormesis and longevity.

It is important to indicate that the rise of NAD+ concentration by NADH-dependent plasma membrane dehydrogenases, which are activated by CR [29-31], would be also key factors to activate sirtuins and thus longevity [32].

Ageing and energy balance: nutrient excess

The other extreme to CR is nutrient excess. Exposure to nutrient excess, frequently characterised experimentally as a 'high-fat diet', has also been shown to reduce longevity [33]. Resveratrol, which is considered a CR mimetic, prevents the obesity-associated diseases and extends obese animal lifespan [34,35]. The classical pathway activated by nutrients is the insulin/insulin-like growth factor-1 (IGF-1) and forkhead box protein (FOXO) pathway, opposing AKT and FOXO to modulate bioenergetics in response to nutrients availability. In metabolic terms, insulin receptor activation is central to glucose homeostasis as it allows cellular uptake of glucose from the circulation into peripheral tissues [36]. In nutrient excess, insulin resistance is often seen, forming the basis for the age-related increase in risk for metabolic disease and type 2 diabetes [37]. Insulin has a role in ageing too, as adipose tissue-specific insulin receptor knockout mice have been shown to extend longevity [38].

An increasing amount of data now suggests that the mammalian target of rapamycin (mTor) pathway is involved in linking nutrient exposure to insulin resistance and ageing. mTor forms two separate complexes (known as mTORC1 or mTORC2) that have distinct biological activities. mTORC1 is activated by nutrient excess [39] and drives biogenesis mediated by the mTORC1 effector, S6K1 [40]. Alongside this emerging role in nutrient sensing and metabolism, mTor has a well-defined role in cell growth and ageing [41-43]. Interestingly, S6K1 $^{-/-}$ mice exhibit similar gene expression profiles to those of calorie restricted mice, with females showing extended longevity and reduced age-related diseases [44]. Reduction of mTORC1 activity in genetic mouse models is also associated with a reduction in age-related cancers [44,45]. This provides further linkage between absence of an enzyme which regulates response to nutrient excess, and successful ageing.

Homologues of the insulin/IGF-1 receptor and its associated signalling molecules, including daf-2, age-1, daf-16 have been associated with changes in longevity in *C elegans* by a number of authors [46,47]. Similar genes have been identified in yeast, fruit flies and mice, confirming the central role of this pathway in the ageing process. Evidence suggests that these long-lived mutants, ranging

from yeast to mice, share important characteristics, including decreased insulin signalling, increased insulin sensitivity [48], and reduced circulating IGF-1 levels [46,49]. These observations strongly suggest that the insulin/IGF-1 pathway might possibly be fundamental to the process of aging in lower and higher organisms, a theory which is borne out by repeated studies into the actions of FOXO family members [50-52].

Does brown adipose tissue hold the key to ageing and metabolism?

There is one particular tissue of mammalian bodies that might potentially provide a decisive and exploitable link between energy balance and ageing. Brown adipose tissue (BAT) has developed as an essential thermoregulatory effector, by facilitating the dissipation of stored energy through the production of heat during the challenge of low environmental temperatures [53]. The actions of BAT are essentially antagonistic to the other main from of adipose tissue, white adipose tissue (WAT) which is predominantly responsible for storing excess energy as triglycerides. The thermogenic ability of BAT is attributable to the high mitochondrial content mediating proton transfer across mitochondrial membranes to produce ATP, in the absence of ATP production excess energy stored in the protons is leaked via uncoupling protein 1 (UCP-1) and released as heat, inducing "non-shivering" thermogenesis [54]. Consequently BAT was until recently thought to be only found in small hibernating mammals and newborns, both of which have a large surface area to body mass ratio and are less capable of maintaining core body temperature [55]. Recent studies utilising both positron emission tomography (PET) and computed tomography (CT) have however identified significant reserves of BAT in adults, using radioactively labelled fluorodeoxyglucose (FDG) as a means of identifying this metabolically active tissue [56-58]. It has been recently discovered that these BAT deposits corresponds to beige adipocytes that are activated through the novel, exercise-induced myokine irisin [59,60]. Recent evidence from our group has demonstrated a significant positive association between plasma irisin levels and telomere length in healthy individuals, highlighting the potential role that modulation of adipose tissue biology has in healthy ageing [61].

These observations, that BAT is present and active in adult humans, represent a huge change in the accepted paradigm of adipose tissue and energy balance. Of potentially key importance is the observation that in mice WAT can be converted to BAT by regulating the expression of a key transcriptional regulator, PRDM16 [62]. This observation opens the door to potential future therapies aimed at recruiting BAT from existing WAT stores in humans, an avenue that would provide a major breakthrough in the treatment of obesity and type 2 diabetes.

In a breakthrough study, the beneficial effects of enhanced BAT and UCP1 activity on longevity was confirmed when a study conducted by Molina et al. reported that mice carrying additional copies of the tumour suppressor gene phosphatase and tensin homolog (Pten), have hyperactive BAT and high levels of UCP1 [63]. This increase in BAT levels was seen to be orchestrated by the PI3K/AKt/Foxo pathway and activation of UCP1 transcriptional promoter PPARγ coactivator 1α. This increase in energy expenditure protected the mice from onset of metabolic pathologies like obesity and diabetes, and was associated with a significantly prolonged life span. This fascinating study highlights not only the huge potential in targeting this signalling pathway as a future therapy for metabolic disorder and ageing, but also highlights how closely their underlying mechanisms are aligned. For one gene to have such a profound effect on two seemingly distinct biological phenomena suggests that they are actually not distinct but instead are likely to be integrated. In correcting the dysregulated energy balance associated with obesity, extended lifespan can be achieved.

Conclusion

Growing evidence supports the notion that energy balance is a key determinant in the process of cellular ageing. With the increasing prevalence of metabolic disorders such as obesity and diabetes, there is an urgent need to improve understanding of the association between metabolic disturbance and biological ageing in humans. Increasing energy expenditure rather than storage during ageing by inducing phenotype-switch in adipose tissue may offer a promising strategy.

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