Could glucose be a proaging factor?

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Abstract

There is an ever-increasing scientific interest for the interplay between cell’s environment and the aging process. Although it is known that calorie restriction affects longevity, the exact molecular mechanisms through which nutrients influence various cell signalling/modulators of lifespan remain a largely unresolved issue. Among nutrients, glucose constitutes an evolutionarily stable, precious metabolic fuel, which is catabolized through glycolytic pathway providing energy in the form of ATP and consuming NAD. Accumulating evidence shows that among the important regulators of aging process are autophagy, sirtuin activity and oxidative stress. In light of recent work indicating that glucose availability decreases lifespan whilst impaired glucose metabolism extends life expectancy, the present article deals with the potential role of glucose in the aging process by regulating – directly through its metabolism or indirectly through insulin secretion – autophagy, sirtuins as well as other modulators of aging like oxidative stress and advanced glycation end-products (AGEs).

Keywords: AGES • aging • autophagy • glucose • glycolysis • mTOR signalling • oxidative stress • sirtuins

Introduction

Aging is a complex, multi-factorial process and numerous aging theories have been proposed. Evolutionarily conserved genes and pathways have been shown to regulate lifespan in mammals. Many gene products known to affect lifespan are intimately involved in the control of energy metabolism including the fuel sensor AMP-activated protein kinase (AMPK) [1], while the lack of klotho gene expression – an important gene for the maintenance of normal energy homeostasis – is characterized by various systemic phenotypes resembling human aging [2].

Although it is clear that our genes influence aging and longevity, how genes interplay with environmental factors (i.e. nutrition, exercise, stress) and how exactly this takes place on a molecular level is still only partially understood and remains a big challenge for scientists.

Glucose, the major form in which carbohydrates absorbed from the intestinal tract is presented to the cells constitutes a very important energy source for the body, serving for some tissues as a vital metabolic fuel; its catabolic pathway, glycolysis, represents an ancient process employed by all body cells to extract part of the chemical energy inherent in the glucose molecule.

In view of current data supporting that glucose availability decreases Caenorhabditis elegans lifespan whereas impaired glucose metabolism extends life expectancy [3], a question arises: could this precious fuel, glucose and its catabolic pathway, glycolysis, be implicated in the aging process?

Here, we briefly discuss how glucose could directly (through its metabolism) or indirectly (by provoking insulin secretion) affect two of the main regulators of the aging process, autophagic and sirtuin activity, as well as other factors involved in aging such as oxidative stress and advanced glycation end-products (AGEs).

Autophagy

Autophagy is a process of degradation and recycling of most long-lived proteins, biological membranes, macromolecules and entire organelles like mitochondria, ribosomes etc., thus playing a crucial role in homeostasis of living cells [4]. Autophagy occurs constitutively at low levels even under normal growth conditions and it seems that baseline autophagy is critical for intracellular clearance. Various human pathologies are associated with decreased autophagic activity, especially in non-dividing cells of the nervous system.
and muscle systems where turnover of long-lived intracellular proteins and organelles may be very important. On the other hand, augmented autophagic activity in aging organisms can have preventive potential [5]. Calorie restriction-induced autophagy has a well-documented effect in extending life expectancy in mammals [6].

It is well known that extracellular glucose levels are connected to cell metabolism, at least in part, through insulin signalling. Insulin, whose secretion is triggered by glucose levels, is thought to be one of the major suppressive factors for autophagy. Interestingly, decreased insulin signalling is linked to enhanced longevity in worms, flies and mice [7], posing that insulin resistance might be a defence mechanism against aging. Insulin receptor activation leads to the phosphorylation of key tyrosine residues on insulin receptor substrate (IRS) proteins, resulting, in turn, in a phosphatidylinositol-3 kinase (PI3K)/- phosphoinositide-dependent protein kinase 1 (PDK1)- / serine-threonine kinase PKB (Akt)- and mammalian target of rapamycin (mTOR)-mediated suppression of autophagy [8] (Fig. 1). The rate of phosphorylation of the insulin receptor kinase domain and several downstream targets including the phosphatidylinositol phosphates, Akt1 and mTOR is determined by the balance between kinase and phosphatase activities. Notably, in the presence of adenosine-5'-triphosphate (ATP) and hydrogen peroxide, which both can be produced by increased glucose intake [9], the insulin receptor kinase domain is phosphorylated at its catalytic site and thereby rendered catalytically active even in the absence of insulin [10] Fig. 1. In contrast, under ATP privation, the AMPK phosphorylates and potentiates tuberous sclerosis protein 2 (TSC2), which inhibits mTOR in combination with TSC1 (hamartin) [11] (Fig. 1). Interestingly, an over-expression of an AMPK alpha subunit (aak-2) in Caenorhabditis elegans has been shown to increase lifespan [1].

Thus, glucose could activate insulin receptor signalling pathway either via induction of insulin secretion by β cells or even in the absence of insulin through increased ATP and hydrogen peroxide production, hence leading to an activated mTOR complex which, by acting on the Atg1 kinase complex, inhibits several steps in autophagosome formation [12]. To this end, mTOR has been shown to affect negatively lifespan [13].

Sirtuins

Among the genes that have been reported to regulate aging in different species are SIR2 and its functional orthologs, sirtuins. Sirtuin proteins are a family of protein deacetylases, which control a diverse array of pathways involved in the aging process [14]. They can forestall aging by stabilizing the rDNA locus [15] and recently have been found to promote mitochondrial biogenesis in liver and muscle through the transcriptional coactivator peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α) [16, 17], and cell survival by deactivating the tumour suppressor p53 [18].

Sirtuins are unique in that they require nicotinamide adenine dinucleotide (NAD) as a cofactor [19, 20]. In a complicated reaction, sirtuins couple lysine deacetylation to NAD hydrolysis, yielding O-acetyl-ADP-ribose and nicotinamide [20]. As such, sirtuin activity seems to be governed by cellular [NAD]/[NADH] ratios and respond to changes in cellular metabolism [21, 22]. Indeed, recent studies imply that the metabolism of NAD/NADH controls cell senescence and lifespan via regulating sirtuin activity [23, 24].

As mentioned above, glycolysis is used by all body cells to obtain part of the chemical energy entrapped in the glucose molecule. Glycolytic pathway is known to lead to the net production of ATP, consuming NAD during the metabolism of glyceraldehyde-3-phosphate to 1, 3-diphosphoglycerate and NADH (as products). An increased glycolytic activity would tend to provoke an accumulation of NADH and lower NAD availability, resulting in a decreased sirtuin activity (Fig. 1).

Nonetheless, this is not the only mode of interplay between glucose and sirtuin activity. A recent study suggested that mTOR inhibition promotes longevity by re-localizing two transcription factors, Msn2p and Msn4p, from the cytoplasm to the nucleus, whereby they stimulate expression of the nicotinamidase gene PNC1, a modulator of sirtuin activity [25] (Fig. 1). Consequently, a glucose challenge, by potentiation of insulin/insulin receptor signalling cascade could down-regulate sirtuin activity through mTOR signalling.

In conclusion, an insulin-dependent or independent high-intracellular glucose offer in combination with a hyperactivation of glycolytic pathway could down-regulate autophagy (through insulin receptor signalling cascade) and sirtuin activity (either via insulin receptor signalling cascade or through decreased NAD levels) at the same time.

Oxidative stress and AGES

A progressive rise of oxidative stress and related inflammatory reaction appears to play a crucial role in the aging process and many age-related diseases. Glucose and glycolysis have also been implicated in the induction of oxidative stress.

Indeed, in an increased intracellular glucose offer, due to continuous ATP synthesis via increased glycolysis, less ATP is required from mitochondrial function, so that the decreased supply of electrons (as acetyl-CoA or from NADH) to the electron transport chain would tend to produce more incompletely reduced oxygen species, that is oxygen-free radicals. Any increased intramitochondrial reactive oxygen species (ROS) production could also increase the probability of mitochondrial dysfunction leading to a vicious cycle [26] (Fig. 1). Schultz et al. [3] found that glucose deprivation in Caenorhabditis elegans induced a mild oxidative stress – by ROS formation –, which could promote the development of antioxidant defence mechanisms that protect the organism from oxidative molecular damage associated with aging. On the other hand, recent studies have shown that glucose challenge induced a consistent increase in ROS generation by human
polymorphonuclear and mononuclear leucocytes [9], an effect that was not produced by equicaloric amounts of alcohol [27]. Moreover, glucose challenge increased intracellular NF-κB [26], a master regulator of inflammation-aging process, as well as other contributors to aging like oxidative stress and advanced glycation end-products (AGEs). Insulin receptor activation leads to a phosphatidylinositol-3 kinase (PI3K)-/phosphoinositide-dependent protein kinase 1 (PDK1)-/serine-threonine kinase PKB (Akt)- and mammalian target of rapamycin (mTOR)-mediated suppression of autophagy. In the presence of adenosine-5’-triphosphate (ATP) and hydrogen peroxide, which both can be produced by increased glycolysis, the insulin receptor can be activated even in the absence of insulin. Under ATP privation through decreased intracellular glucose offer, the AMP-activated protein kinase (AMPK) phosphorylates and potentiates tuberous sclerosis protein 2 (TSC2) which inhibits mTOR in combination with TSC1 (hamartin). An increased glycolytic activity would tend to provoke an accumulation of NADH and lower NAD availability, resulting in decreased sirtuin activity. mTOR can also suppress sirtuin activity through inhibition of nicotinamide gene (PNC1) expression. Finally, an increased intracellular glucose offer can lead via increased glycolysis to: (i) mitochondrial dysfunction and oxidative stress (increased reactive oxygen species) due to continuous ATP synthesis, and (ii) accumulation of highly toxic advanced glycation end-products (AGEs) which can further provoke oxidative stress. GLUT4, glucose transporter 4; IRS, insulin receptor substrate.

An hyperactivation of glycolytic pathway could also lead to accumulation of glyceraldehyde-3-phosphate and dihydroxyacetone phosphate (DHAP), which both can glycate proteins and putrefied to methylglyoxal, a highly toxic and very reactive glycat ing agent [30]. It is known that protein AGEs are increased under conditions of hyperglycaemia [31]. Protein AGEs can themselves induce inflammatory conditions and provoke production of ROS, which can further influence cell function (Fig. 1). Specifically, methylglyoxal has been shown to trigger many of the deleterious physiological and biochemical changes characteristic of the aged phenotype, including increased ROS generation, mitochondrial dysfunction, apoptosis and inhibition of cell division [32].
According to recent reports, increased dietary AGE intake accelerates aging and decreases lifespan, whereas decreasing dietary AGE intake can preserve defense functions against oxidative stress, decrease tissue damage in humans and extend lifespan in mice [33-34]. It is therefore conceivable that decreasing metabolically generated protein AGES could help lowering the overall AGE load and could have beneficial effects by suppressing aging and extending lifespan.

Moreover, when the sticky ends of AGES adhere to neighboring proteins, they form permanent, disabling cross-links. Proteases, which normally broke down damaged proteins, are inhibited in the presence of cross-linkage, thus leading to accumulation of damaged protein molecules. Indeed, atherosclerosis, cataract, skin alterations, renal dysfunction are some of the age-related conditions that are partially attributed to glycation processes. 

Conclusions

Since until very recently the organisms’ main problem was dealing with nutrient deprivation (rather than the current surfeit); it was more economical during times of caloric restriction to shut off reproduction, decrease hormonal activity and decrease metabolic activity until nutrients again became available. It was evolutionarily more advantageous to keep the organism alive longer when it was starving than to expend energy reproducing and thus create more competition for limited nutrients.

Indeed, since the 1930s it is known that limiting the food consumed by laboratory rodents increases their lifespan [37]. Eighty years later, having our knowledge in the interaction between nutrients and life expectancy widen, we may say that one of this nutrients, glucose, could be a pro-aging factor by affecting important regulators of the aging process, while restriction of glucose could trigger physiological changes linked to health and longevity.

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