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OPINION

Energy metabolism, altered proteins, sirtuins and ageing: converging mechanisms?

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Abstract The predominant molecular symptom of ageing is the accumulation of altered gene products. Nutritional studies show that ageing in animals can be significantly influenced by dietary restriction. Genetics has revealed that ageing may be controlled by changes in intracellular NAD/NADH ratio regulating sirtuin activity. Physiological and other approaches indicate that mitochondria may also regulate ageing. A mechanism is proposed which links diet, exercise and mitochondria-dependent changes in NAD/NADH ratio to intracellular generation of altered proteins. It is suggested that ad libitum feeding conditions decrease NAD availability which also decreases metabolism of the triose phosphate glycolytic intermediates, glyceraldehyde-3-phosphate and dihydroxyacetone-phosphate, which can spontaneously decompose into methylglyoxal (MG). MG is a highly toxic glycating agent and a major source of protein advanced-glycosylation end-products (AGEs). MG and AGEs can induce mitochondrial dysfunction and formation of reactive oxygen species (ROS), as well as affect gene expression and intracellular signalling. In dietary restriction–induced fasting, NADH would be oxidised and NAD regenerated via mitochondrial action. This would not only activate sirtuins and extend lifespan but also suppress MG formation. This proposal can also explain the apparent paradox whereby increased aerobic activity suppresses formation of glycoxidized proteins and extends lifespan. Variation in mitochondrial DNA composition and consequent mutation rate, arising from dietary-controlled differences in DNA precursor ratios, could also contribute to tissue differences in age-related mitochondrial dysfunction.

Keywords NAD · NADH · Glycolysis · Methylglyoxal · Dietary restriction · Altered proteins · Deacetylases · Ageing

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NAD and life-span

Genetic studies using a range of organisms have indicated that enzymes called sirtuins are linked to the control of ageing and life-span (Longo and Kennedy 2006; Leibiger and Berggren 2006; Lin and Guarente 2003). Sirtuins catalyse NAD-dependent deacetylation of histones (and other proteins) with the concomitant release of nicotimanide and O-acetyl-ADP-ribose (Howitz et al. 2003). Other studies have suggested that metabolism of the redox couple NAD/NADH provides a link between sirtuin activity and the control of cell senescence and organism life-span (Denu 2003, 2007; Belenky et al. 2007; Bordone and Guarente 2005): NAD-dependent

protein deacetylation helps maintain the juvenile phenotype, whereas inhibition of deacetylation activity by NADH or nicotinamide, or by NAD unavailability, promote the onset of cellular aging and decrease organism lifespan.

Ageing, dietary restriction and NAD

Ageing can be delayed in various organisms by dietary restriction (DR) induced by a permanent decrease in calorie intake (called caloric restriction—CR). Recent observations have shown that an intermittent feeding (IF) protocol, which need not involve any overall reduction in calorie intake, can also delay ageing (Martin et al. 2006; Masternak et al. 2005; Mattson and Wan 2005). The mechanisms by which DR delays ageing and increases life-span are far from completely understood (Sinclair 2005). It is likely, however, that both CR and IF promote similar effects on the frequency of glycolysis and subsequent fasting periods (Hipkiss 2006a and 2007), i.e. glycolysis would be discontinuous, only operating post-prandialy. In contrast, glycolysis would be almost continuous under ad libitum (AL) feeding conditions. It is suggested that during the periods of fasting (induced by either CR or IF) the NAD/NADH ratio would differ from that prevailing in the AL case where fasting would be unlikely or negligible. In the AL condition, continuous glycolytic throughput would tend to provoke an accumulation of NADH and lower NAD availability, whereas the CR- and IF-induced fasting would decrease glycolytic NAD demand and increase NADH oxidation and NAD regeneration.

Ageing and accumulation of altered proteins

At the biochemical level ageing is characterized by the accumulation of altered protein molecules. The changes in protein structure result from intrinsic polypeptide instability as well as the actions of deleterious endogenous and exogenous agents (see Hipkiss 2006b; Schoneich 2006 and refs. therein). As yet it is unclear how changes in NAD metabolism might induce generation of altered proteins which characterise the aged phenotype.

Protein glycation and ageing

Formation of protein advanced glycation end-products (AGEs) is an important consequence of ageing and is increased particularly under conditions of uncontrolled glucose metabolism (e.g. hyperglycaemia) (see Ahmed and Thornally 2007; Thornalley 2007 and refs. therein for recent reviews). Protein AGEs can themselves induce inflammatory conditions and provoke production of reactive oxygen species (ROS) which can further compromise cell function. Indeed recent studies have shown that decreasing dietary AGE intake preserves defence functions against oxidative stress and decreases tissue damage in humans, and extends lifespan in mice, while increasing dietary AGE intake is correspondingly deleterious and accelerates ageing and decreases lifespan (Cai et al. 2007; Uribarri et al. 2007a, b). Hence it is at least conceivable that decreasing metabolically-generated protein AGEs could help decrease the overall AGE load and could have beneficial effects by suppressing ageing and extending lifespan.

NAD and accumulation of methylglyoxal, an endogenous glycating agent

NAD is essential for the metabolism of the glycolytic intermediate glyceraldehyde-3-phosphate (G3P) via the action of glyceraldehyde-3-phosphate dehydrogenase (GAPDH), generating 1,3-diphosphoglycerate (1,3DPG) and NADH as products. It is argued above that in the AL condition, glycolysis would be continuous, which would tend to lower NAD levels and raise NADH levels. This would occur especially should mitochondrial-mediated NADH re-oxidation to NAD be correspondingly lowered to compensate for the extra ATP synthesised via glycolysis, assuming cellular ATP demand remains unchanged. Limitation of NAD availability would lower GAPDH activity and promote an accumulation of G3P. The immediate precursor of G3P is dihydroxyacetone phosphate (DHAP); both of these trioses can glycate proteins. More importantly, however, is the fact that both G3P and DHAP can spontaneously decompose into methylglyoxal (MG), a highly toxic and very reactive glycating agent. It is likely therefore that changes in NAD availability could strongly influence MG production.

It has previously been proposed that differences in glycolytic frequency could help explain why dietary restriction delays cellular and organism aging, possibly due to decreased MG generation during DR conditions (Hipkiss 2006a). MG is a highly active glycating agent which is thought to be responsible for the increased protein/lipid glycation detected during hyperglycaemic conditions and for much of the protein/lipid glycation associated with diabetic complications (Ahmed and Thornalley 2007; Thornalley 2007). Although MG is a normal cellular constituent, its excessive production is deleterious (plasma MG levels are raised to around 800 nmol/l in young diabetics compared to about 400 nmol/l in young non-diabetic subjects, (Han et al. 2007)). Importantly, MG can induce 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 (see Hipkiss 2006a and refs therein).

A number of studies, some very recent, reinforce the notion that changes in cellular MG content are important determinants of the formation of altered protein that characterise senescence (Gomes et al. 2006). Even at non-toxic concentrations, MG can influence cell proliferation by forming adducts with growth factor receptors (Cantero et al. 2007). MG can also inhibit the activity of GAPDH (Lee et al. 2005), causing triose phosphate accumulation and thereby increasing MG generation, and so inducing a highly deleterious cycle. MG can induce apoptosis (Nicolay et al. 2006) and also affect gene expression and signal transduction, at least in cultured cells (Du et al. 2003; Yao et al. 2006; Ramasamy et al. 2006). Two studies in Drosophila have shown that mutation in triosephosphate isomerase (the enzyme which converts DHAP into G3P, preceding GAPDH in the glycolytic pathway, and which is known to undergo age-related post-synthetic modification in vivo (Gracy et al. 1990)) is highly deleterious, causing paralysis, neurodegeneration and decreases life-span (Gnerer et al. 2006; Celotto et al. 2006), possibly because of MG accumulation. Human studies have shown that a deficiency in triosephosphate isomerase activity, causes increases in the levels of both DHAP (up to 20-fold (Schneider 2000)) and MG (Ahmed et al. 2003), and induces neuromuscular degeneration and early death (Schneider et al. 1965; Valentine 1966). Other studies have shown that MG induces apoptosis in neutrophils (Gawlowski et al. 2007), inhibits extracellular matrix remodelling (Chong et al. 2007) and can interfere with the stress response (Oya-Ito et al. 2006) by suppressing NF-kappaB-responsive gene activation (Laga et al. 2007).

Hence it is reasonable to suggest that any increased MG generated in AL fed animals, compared to animals subjected to CR or IF, could make a significant contribution to cellular dysfunction. During the fasting periods in DR animals, NADH generated during glycolysis would be oxidized mitochondrially for ATP production, and NAD would be regenerated thereby allowing continued G3P metabolism, and preventing triose phosphate accumulation and consequently suppressing MG generation. This condition would decrease MG-induced macromolecular glycoxidation, mitochondrial damage, dysfunctional signalling and gene expression, as described above. Such a scenario is consistent with the findings that raising NAD levels, or lowering NADH levels by increasing its oxidation, also promote sirtuin activation, with concomitant beneficial effects on cell survival etc. Table 1 illustrates the interrelationship and overlap between sirtuin regulation, generation of altered proteins and mitochondrial activity, exerted by metabolic effects on NAD and NADH levels.

Any situation such as fasting which maintains NAD levels, either via regeneration from NADH, or by synthesis de novo or via a scavenging pathway, would facilitate metabolism of the MG precursors G3P and DHAP, and so decrease the incidence of MG-induced macromolecular damage. The increase in free-radical-mediated damage which occurs during AL feeding, compared to the CR and IF conditions, might occur as a result of not only MG-induced generation of ROS following its reaction with proteins etc., but also via plasma membrane-mediated NAD(P)H-oxidase activity. Furthermore, because less ATP is required from mitochondrial function due to continuous ATP synthesis via glycolysis in the AL-fed state, the decreased supply of electrons (as acetyl-CoA or from NADH) to the electron transport chain would tend to produce more incompletely reduced oxygen moieties i.e. oxygen free-radicals. Any increased intra-mitochondrial ROS production could also increase the probability of mitochondrial dysfunction.

Protection against MG is afforded by the glyoxalase system which consists of two enzymes; glyoxalase I (GLX I), which uses glutathione to

Table 1 Predicted effects of aerobic exercise and fasting induced by caloric restriction or intermittent feeding, on NAD and NADH levels, methylglyoxal (MG) levels, mitochondrial (mito) activity and sirtuin activity

Conditions	NAD	NADH	MG	Mito activity	Sirtuin activity
Ad libitum fed	Low	High	High	Lowered	Lowered
Fasting	High	Low	Low	Increased	Increased
Aerobic exercise	High	Low	Low	Increased	Increased

Increased MG levels are partly responsible for the increased generation of altered proteins that accompanies ageing

convert MG to a D-lactoyl-glutathione, and glyoxalase II (GLX II), which completes the detoxification by generating D-lactate and reduced glutathione. Over-expression of GLX I can inhibit formation of hyperglycaemia-induced AGEs (Shinohara et al. 1998), while a deficiency in GLX I in humans is associated with increased protein glycation (Miyata et al. 2001). GLX II activity may be rate-limiting in MG detoxification; GLX II over-expression is protective against MG-induced cell death, whilst its deficiency promotes MG-induced cell death (Xu and Chen 2006). It is also interesting that tumour necrosis factor can induce phosphorylation of GLX I which also results in substantial increase in cellular MG (van Herreweghe et al. 2002).

Tissue differences in ageing susceptibility

Tissues appear to age at different rates as shown by the varied incidence of dysfunctional mitochondria between tissues in the same organism. Variation in tissue susceptibility to MG may reside partly in differing levels of the glyoxalase system together with those molecules (glutathione, polyamines, carnosine, creatine, pyridoxamine) which normally exert protective carbonyl scavenging activity towards glycating agents such as MG (Hipkiss 2005; de Arriba et al. 2006).

Dietary-induced effects on metabolism could conceivably also affect mitochondrial DNA composition and hence mitochondrial protein structure and function. It has been found that mitochondrial DNA mutation rate may vary up to three-fold according to the relative concentrations of the four deoxyribonucleoside triphosphates in the nucleotide pool (Song et al. 2005; Mathews and Song 2007). It is possible that dietary changes could affect the composition of the nucleotide pool and thereby affect mitochondrial DNA composition during its synthesis. Pool composition could vary between tissues, and any consequent differences in mitochondrial DNA mutation rate would contribute to tissue-specific age-related mitochondrial change. Thus mitochondrial dysfunction could be either a cause or a consequence of ageing (Hipkiss 2003), depending on the prevailing circumstances.

The beneficial effects of functional mitochondria on NAD regeneration

The recent observations (i) by Belenky et al. (2007) showing that life-span extension in yeast is dependent upon NAD synthesis, (ii) that efficient mitochondrial function was necessary for maximal longevity in yeast (Piper et al. 2006), and (iii) that mitochondrial uncoupling, which increases NADH oxidation, decreases telomere damage and delays senescence in cultured human fibroblasts (Passos et al. 2007), are observations entirely consistent with the above proposal. The proposed beneficial effects of NADH oxidation to regenerate NAD via mitochondrial function would also help explain how aerobic exercise may delay development of the aged phenotype including production of altered proteins, as well as resolve the apparent paradox that increased oxygen utilization suppresses age-related change. The efficient regeneration of NAD via effective mitochondrial function is also consistent with mitochondrial ageing theories which postulate that mitochondrial dysfunction is key to the onset of ageing.

Also consistent with the present proposal are the very recent findings of Smith et al. (2007) who concluded that, in the yeast Saccharomyces cerevisiae at least, elevated respiration is an important determinant of chronological longevity. They observed that growth on non-fermentable carbon sources, which forced the cells to employ respiration exclusively, extended lifespan, but which caloric restriction did not further enhance. This again illustrates, simplistically

perhaps, the potential anti-ageing functions of aerobic respiration and the deleterious effects of glycolysis, both possibly mediated via changes NAD and NADH levels, which in turn regulate MG generation. Controversially, however, these authors also found that caloric restriction-mediated lifespan extension occurred independently of sirtuin activity in Saccharomyces cerevisiae.

Other functions induced by DR

Ageing is a complex phenomenon. It is likely that the rate-limiting event which increases cellular and hence organism vulnerability to death may vary according to circumstances. For example anti-oxidant functions may not be limiting in conditions where oxidative stress is not involved. There are an increasing number of findings suggesting that proteolytic dysfunction involving either proteasomes or autophagy cause altered protein to accumulate and compromise cell survival and which can be affected by dietary restriction (Bergamini et al. 2003). Conversely activation of autophagy by inhibiting the target of rapamycin (TOR) signalling pathway can increase lifespan, at least in yeast (Bonawitz et al. 2007) and a nematode worm (Henderson et al. 2006). The recent observation that the sirtuin-like activity, histone deacetylase 6 (HDAC6), may provide a mechanistic link between the autophagic and ubiquitin-proteasome proteolytic systems in Drosophila (Pandey et al. 2007), and the observation that up-regulation of neuronal sirtuin1 activity elevates the activity of the α-protease and prevents accumulation of the amyloid peptide (Qin et al. 2006), support the idea that both formation and degradation of aberrant proteins are important for control of ageing and related disorders.

Conclusion

It is proposed that dietary-induced changes in NAD and NADH levels, as revealed by their regulation of sirtuin activity, may also control the concentration of deleterious glycolytic intermediates G3P and DHAP, and thereby also control formation of MG and generation of protein AGEs. The accumulation of MG and protein AGEs may compromise tissue function including mitochondrial activity and thereby contribute to organism ageing. Conversely, conditions that stimulate mitochondrial function will help regenerate NAD, maintain sirtuin activity and decrease formation of protein AGEs, intra- and extra-mitochondrial ROS can thereby delay ageing onset.

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