Mini review

On the mechanisms of ageing suppression by dietary restriction—is persistent glycolysis the problem?

Alan R. Hipkiss *

Centre for Experimental Therapeutics, William Harvey Research Institute, John Vane Science Centre, Bart’s and the London Queen Mary’s School of Medicine and Dentistry, Charterhouse Square, London EC1M 6BQ, UK

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Abstract

The mechanism(s) by which dietary restriction (DR) suppresses ageing and onset of age-related pathologies are discussed in relation to frequency of glycolysis, and the reactivity of glycolytic intermediates. Most glycolytic intermediates are potentially toxic and readily modify (i.e. glycate) proteins and other macromolecules non-enzymically. Attention is drawn to the reactivity of methyglyoxal (MG) which is formed predominantly from the glycolytic intermediates dihydroxyacetone- and glyceraldehyde-3-phosphates. MG rapidly glycates proteins, damages mitochondria and induces a pro-oxidant state, similar to that observed in aged cells. It is suggested that because DR animals’ energy metabolism is less glycolytic than in those fed ad libitum, intracellular MG levels are lowered by DR. The decreased glycolysis during DR may delay senescence by lowering intracellular MG concentration compared to ad libitum-fed animals. Because of the reactivity MG and glycolytic intermediates, occasional glycolysis could be hormetic where glyoxalase, carnosine synthetase and ornithine decarboxylase are upregulated to control cellular MG concentration. It is suggested that in ad libitum-fed animals persistent glycolysis permanently raises MG levels which progressively overwhelm protective processes, particularly in non-mitotic tissues, to create the senescent state earlier than in DR animals. The possible impact of diet and intracellular glycating agents on age-related mitochondrial dysfunction is also discussed.

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1. Mechanistic or evolutionary explanations of dietary restriction effects on senescence?

The papers by Partridge and Brand (2005), Guarente (2005), Kirkwood and Shanley (2005), Masoro (2005), Merry (2005), Sinclair (2005), Spindler (2005), Walker et al. (2005) and Yu (2005) recently published in this journal provide a stimulating account of the effects and possible underlying mechanisms of dietary restriction (DR) on ageing in a variety of organisms. It is reasonable to anticipate that the biological adaptation induced by DR is based on identifiable physiological and biochemical events. In a study of the energy metabolism in rats McCarter and Palmer (1992) revealed significant differences between animals subjected to DR and those fed ad libitum. Respiratory quotient (RQ) data indicated that ad libitum-fed animals were predominantly glycolytic (RQ = 0.89) throughout a 24 h period. In contrast, although the DR rats’ metabolism was very glycolytic (RQ = 0.9) immediately after feeding, thereafter the animals’ RQ declined to around 0.80 for the remainder of the day, indicating that during the fasting period their energy derived predominantly from aerobic lipid metabolism and that glycolysis was suppressed. Consequently it can be argued that the beneficial effects that DR induces could derive, at least in part, from suppression of glycolysis. Indeed in their discussion of possible mechanisms of DR, Walker et al. (2005) and Partridge and Brand (2005) briefly raise the question of whether the shortened life-span of well-fed animals results from food toxicity. It is this idea of food (and metabolite) toxicity, specifically whether glycolysis is potentially deleterious but possibly hormetic, which I explore here.

* Tel.: +44 20 7882 6032; fax: +44 20 7882 6037.
  E-mail address: alanandjill@lineone.net.

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2. Could infrequency of glycolysis play a role when ageing and related pathologies are delayed by dietary restriction?

Living is molecularly dangerous, as evidenced by the plethora of homeostatic processes (anti-oxidants—enzymatic and non-enzymatic, DNA repair enzymes, and various proteases, etc.) necessary for an organism’s survival, even for a short period of time. The toxic effects of oxygen, especially when present in excess, have been long discussed as a cause or contributor to ageing in general, and mitochondria proposed as the major source of age-associated cellular disorder/dysfunction via increased generation of reactive oxygen species (ROS) within them. It should be pointed out, however, that the other major pathway in energy metabolism, glycolysis, is also a potential source of endogenous molecular toxicity. The majority of glycolytic intermediates, being either aldehydes or ketones, possess reactive carbonyl groups and are therefore potentially deleterious. They are capable of modifying protein amino groups via mechanisms similar to non-enzymic glycosylation (glycation) (Kikuchi et al., 2003). Glucose possesses a very low reactivity towards protein amino groups, etc., due to the fact that the sugar is present predominantly in the un-reactive ring form (only in the chain form the aldohexose group free to react), whereas all glycolytic intermediates are more reactive. Most reactive of all are the trioses glyceraldehyde-3-phosphate and dihydroxyacetone-phosphate; both can glycate proteins very rapidly to give brown products (called advanced glycosylation end-products or AGEs). There is a substantial body of evidence illustrating the deleterious effects of glycation in general on proteins (Baynes, 2000; Kikuchi et al., 2003), including mitochondrial proteins (Kil et al., 2004) and DNA (Suji and Sivakami, 2004). Recent studies with mutant nematodes have shown a close relationship between extended life-span and suppression of production of age pigment material which is likely to contain AGEs, whereas higher levels of age pigment identified animals that age poorly (Gerstbrein et al., 2005). These observations again suggest an association between ageing, glycation and its control.

Glycation plays a major role in many age-related pathologies, especially diabetes (Brownlee, 2001; Alt et al., 2004) and its secondary complications (Koschinsky et al., 1997; Ahmed, 2005), as well as brain ageing (Dukic-Stefanovic et al., 2001) and Alzheimer’s disease (Kikuchi et al., 2003; Ahmed et al., 2005a; Reddy et al., 2002). Miyajima et al. (2005) have shown that glyceraldehyde-generated AGEs induce vascular endothelial cell growth factor (VEGF) expression but reduce glial cell derived neurotrophic factor (GDNF) production, which are likely to increase blood brain barrier permeability, another symptom of ageing.

3. Methyglyoxal: a source of age-related dysfunction?

Even more reactive than glyceraldehyde- and dihydroxyacetone-phosphates is a glycolytic by-product methyglyoxal (MG) (Chaplen, 1998) which is toxic even when administered at low levels (Ankrah and Appiah-Opong, 1999). Most MG in mammalian cells is generated, both spontaneously and enzymically, from glyceraldehyde-3-phosphate and dihydroxyacetone-phosphate via phosphate elimination from the 1,2-enediol-3-phosphate. Additional sources of MG are amino acids (threonine and glycine) and fatty acids. There is a growing body of evidence showing that MG is highly deleterious (Kalapos, 1999). It is cytotoxic (Kikuchi et al., 2003; Maeta et al., 2005a) being capable of glycating and cross-linking proteins (Hippkiss and Chana, 1998; Ahmed et al., 2005; Miller et al., 2003), as well as causing damage to lipids and DNA (Pischetsrieder et al., 1999; Roberts et al., 2002, 2003; Kang, 2003). MG has a pro-oxidant effect in smooth muscle cells (Wu, 2005) and cortical neurones (Kikuchi et al., 2003). It inhibits heart mitochondria (SinhaRoy et al., 2005), reacts with arginines residues of mitochondrial permeability transition pore proteins (Johans et al., 2005), provokes organelle dysfunction and increases ROS production (Rosca et al., 2005). Yim et al. (2001) suggest that glycation of proteins with MG creates active centres for one-electron oxidation–reduction reactions and consequent generation of ROS. MG can also inactivate glutathione peroxidase irreversibly (Park et al., 2003), which is very likely to increase cellular peroxide concentration and provoke oxidative damage.

Specific roles of MG in spontaneous hypertension (Wang et al., 2004) and diabetic complications have been proposed by Mathys et al. (2002), whilst Berlanga et al. (2005) have recently shown that prolonged MG administration can induce microvascular damage and other diabetes-like complications even within a normo-glycaemic context. Gomes et al. (2004) have found that MG may be causatively involved in familial amyloidotic polyneuropathy.

The rate of MG formation has been calculated to be between 0.1 and 0.4% of the glycolytic flux and the amount of free intracellular MG appears to range from 0.16 to 2.4 μM, whilst reversibly bound MG may be 2–3 orders of magnitude higher (Chaplen, 1998). The intracellular MG concentration is therefore determined by the rate and persistence of glycolytic activity (Beisswenger et al., 2001; Nemet et al., 2005). It can be argued, therefore, that continuous glycolysis in ad libitum-fed animals (McCarter and Palmer, 1992) would generate more MG than in the DR condition where glycolysis is reduced in duration because of the restricted availability of food in the latter state. Low cellular proliferation rates also seem to increase cellular MG concentrations, most likely because of decreased use of glycolytic intermediates as precursors for anabolic activities such as DNA synthesis (Chaplen, 1998), which would exacerbate the condition in post-mitotic cells, particularly in ad libitum-fed adult animals. Furthermore, deficiency or inactivation of glyceraldehyde-3-phosphate dehydrogenase (GAPDH), the enzyme which converts dihydroxyacetone-3-phosphate and glyceraldehyde-3-phosphate into the far less toxic 3-phosphoglyceric acid, can promote a large increase in MG concentration and glycated products (Ahmed et al., 2003); it is noteworthy that GAPDH is particularly susceptible to glycation by its substrates glyceraldehyde- and dihydroxyacetone-phosphates (Morgan et al., 2002).
As detailed above, MG can provoke many, or most, of the deleterious biochemical changes that accompany normal ageing (protein carbonyl groups and cross-linking, lipid and DNA damage, ROS, apoptosis). Consequently it is proposed that persistent glycolysis in ad libitum-fed animals is detrimental because of the continuous generation of high levels of MG. Whereas in the DR animals glycolysis is transient with any MG that is generated persisting for only a short period of time. That DR effects on ageing can be also induced by fasting, induced by intermittent (e.g. every other day) feeding, while not involving any decrease in overall caloric intake (Mattson and Wan, 2005; Goodrick et al., 1990; Masternak et al., 2005) is entirely consistent with the proposal that some food component or metabolite is toxic and may be responsible, at least in part, for the earlier onset of ageing in ad libitum-fed animals. As noted by Walker et al. (2005) obesity may not necessary to induce this condition, just excess glycolytic activity may be sufficient.

4. Naturally-occurring protection against MG

Not unexpectedly, protective processes have evolved that ameliorate the deleterious actions of MG; most cells seem to possess glyoxalases (Thornalley, 1993, 2003; Ponces et al., 2003) as well as other aldehyde-scavenging enzymes (Davydov et al., 2004) that convert the toxic agent into less harmful molecules. The expression of glyoxalase 1 in certain areas of the brain may vary during human life-span (Kuhla et al., in press) and erythrocyte glyoxalase 1 deficiency may be associated with a large increase in plasma AGEs (Miyata et al., 2001). Conversely, up-regulation of glyoxalase-1 activity can lower cell-associated MG, and possibly also suppress Alzheimer’s disease (AD) (Chen et al., 2004). Interestingly, DR can attenuate amyloid-β deposition in an AD animal model (Patel et al., 2005) although it remains to be shown what mechanisms best explain this observation.

Non-enzymic scavenging of MG could occur via glutathione, pyridoxamine, thiamine, the polyamines spermine and spermidine and the dipeptide carnosine (see Monnier, 2003 for extensive list). Spermine, spermidine and carnosine, are present at high concentrations in some tissues, carnosine being especially located in long-lived tissues (muscles and nerves), more being present in glycolytic white muscle than in aerobic red muscle (Abe, 2000), consistent with its proposed protection against excess glycolytic intermediates and reactive aldehydes generally (Hipkiss, 1998, 2002, 2005).

Carnosine, pyridoxamine, spermine and spermidine all suppress MG-mediated protein cross-linking (Hipkiss and Chana, 1998; Nagaraj et al., 2002; Gugliucci and Menini, 2003; Gugliucci et al., 2002). Carnosine not only inhibits MG-induced generation of protein carbonyl groups (Brownson and Hipkiss, 2000), but also the cross-linking of MG-modified lysine (Hipkiss and Chana, 1998) and MG-treated ovalbumin to normal proteins. The dipeptide also forms adducts with MG-induced protein-bound carbonyl groups (Brownson and Hipkiss, 2000). Carnosine-acrolein, and -hydroxynonenal (HNE) adducts have been characterised (Aldini et al., 2002; Carini et al., 2003; Liu et al., 2003), one of which (carnosine-HNE) was recently detected in muscle tissue (Orioli et al., in press). Carnosine can also suppress senescence in cultured human fibroblasts (McFarland and Holliday, 1994) and some anti-ageing effects were also observed in mice and fruit flies (Yuneva et al., 1999, 2002). The recent observation by Ruiz et al. (2005) that malondialdehyde–protein–lysine adducts decrease with maximum lifespan in a range of mammals is at least consistent with carnosine’s ability to protect proteins against malondialdehyde-induced damage (Hipkiss et al., 1997) and the apparent positive correlation between tissue carnosine content and lifespan maxima (Hipkiss et al., 1993; Munch et al., 1997). Lee et al. (2005) recently demonstrated that the dipeptide can delay onset of diabetic complications in mice, and Schroder et al., (2004) detected “carnosinylated” aminoaliphid in human muscle. These observations reinforce the proposal that carnosine may indeed protect against reactive carbonyl compounds in vivo (Hipkiss, 1998, 2002).

It is unlikely that carnosine is the sole non-enzymic aldehyde-scavenging agent in vivo. Spermine, spermidine (Gugliucci and Menini, 2003), and pyridoxamine (Onorato et al., 2000) may also perform similar functions, if present in sufficient quantities. Indeed millimolar quantities of spermine are present in nuclei which may protect DNA and histones from glycation (Gugliucci and Menini, 2003). Spermine has also been shown to inhibit formation of the AGE pyrraline during long-term exposure of albumin to glucose (Mendez and Leal, 2004). Pyridoxamine is also an aldehyde scavenger (Amarnath et al., 2004) and MG–pyridoxamine adducts have also been characterised (Nagaraj et al., 2002). Interestingly, a deglycating role for fructosamine-3-kinase has been proposed where the enzyme is suggested to recycle spermine–carbonyl adducts (Gugliucci, 2005); a transglycating mechanism also mediated by fructosamine-3-kinase has been proposed (Szwegold, 2005) in which the sugar-derived component of Maillard reaction product (Schiff’s base) is transferred to taurine, carnosine, anserine or glutathione. Tissue concentrations of polyamines (Gugliucci, 2005) and carnosine (Johnson and Hammer, 1992; Stuerenburg and Kunze, 1999) may also decrease with age, which could increase the potential for MG-induced dysfunction in older animals. However much more needs to be done to substantiate the in vivo participation of these potential aldehyde-scavenging, anti-glycating agents and processes, and whether they change with age.

Non-physiological carbonyl scavengers (aminoguanidine and tenilsetam) can protect human neuroblastoma cells against MG toxicity (Webster et al., 2005), an observation which supports the proposal that physiological agents which form adducts with MG could help control MG toxicity in vivo.

Thiamine, in the form of a lipid-soluble derivative benfotiamine, has also been reported to suppress hyperglycaemic damage in experimental diabetes (Babaei-Jadidi et al., 2003; Hammes et al., 2003). The inhibitory mechanisms apparently involve stimulatory effects on the rate-limiting enzyme in the pentose pathway, transketolase, whose substrates are fructose-6-phosphate and glyceroldehydes-3-phosphate, which would decrease the potential for MG generation.
Additional evidence for an anti-senescence effect of diverting glucose metabolism away from the glycolytic pathway has recently been provided by Maruyama et al. (2005) who showed that the senescence marker protein 30 (SMP30), which decreases during ageing (Fujita et al., 1999) is a gluconolactonase, an enzyme which catalyses the conversion of 6-phosphoglulconolactone to 6-phosphoglucuronate, part of the initial steps in the pentose phosphate pathway which generates pentoses for nucleic acid synthesis and NADPH for reduction of oxidised glutathione. Maruyama et al. (2005) suggest SMP30 deficiency may induce the ageing phenotype and conclude that it may be an anti-ageing protein particularly as SMP30 Hep G2 cell transfectants show enhanced survival (Matsuyama et al., 2004). Whilst these observations may be preliminary they are consistent with the present proposal that decreasing synthesis of MG precursors may help to suppress onset or progression of ageing. It is likely that gluconolactonase normally declines with age co-ordinately with falling growth rates, presumably reflecting the decreased requirement for pentose units for nucleic acid synthesis. It is possible that in the ad libitum-fed animals this fall in requirement for pentose units is not balanced by a decreased intake of precursor material with an increased generation of triose phosphates, and hence MG, as a consequence.

5. DR and hormesis: is glycolysis a stressor?

The hormesis hypotheses outlined by Masoro (2005) and Sinclair (2005) suggest that transient exposure to stress may induce synthesis of long-term protective function(s) against deleterious age-related changes such as protein oxidation and glycation (Verbeke et al., 2000, 2001). I suggest that persistent glycolysis is deleterious due to the generation of MG, but brief periods of glycolysis could be hormetic. In yeast increased glucose uptake was shown to upregulate glyoxalase-I synthesis (Maeta et al., 2005b), while the promoter region of a nematode glyoxalase 1 gene contains an insulin-responsive element and is also controlled by oxidative stress (Sommer et al., 2001), observations consistent with the idea that MG levels are biologically regulated according to dietary and environmental conditions. Leung et al. (2005) found that various glucose degradations products, including MG, induced synthesis of vascular endothelial growth factor and transforming growth factor-β in human peritoneal mesothelial cells which could enhance transformed cell survival, indicating that MG may also initiate signal transduction pathways.

Pyridoxamine may also be synergistic as it can increase glyoxalase activity in erythrocytes (Nagaraj et al., 2002), as well as react directly with MG as described above. Nagaraj et al. (2003) showed that the chaperone functions of the stress proteins α-crystallin and Hsp-27 were enhanced by MG modification, an effect which can be regarded as hormetic, but the degree of extra protection mediated by MG would be limited by the amount of chaperone protein available for modification. Obviously should MG production exceed the amount of chaperone protein present then excess MG generation would be deleterious, as might occur in persistent glycolysis in ad libitum-fed animals.

Another possible hormetic protective activity is the synthesis of carnosine. The dipeptide can suppress MG reactivity by (i) behaving as a glycoxalase 1 mimetic (Battah et al., 2002), (ii) forming adducts with MG (see above), (iii) promoting disaggregation of MG-glycated protein (Seidler et al., 2004) and (iv) when complexed with zinc ions, inducing synthesis of the stress protein hsp72 as observed in rat mucosal tissue (Odashima et al., 2002). Synthesis of carnosine may be metabolically controlled because cAMP has been shown to down-regulate carnosine synthetase by up to 80% in astroglia-rich primary cultures (Schulz et al., 1989). Consequently it can be argued that short-term glycolysis would induce carnosine synthesis, whilst persistent glycolysis would markedly increase intracellular glycation potential (via MG) towards proteins, lipids and DNA, possibly overwhelming the protective activities of glyoxalase, carnosine, pyridoxamine andspermine and other unidentified protective functions. Interestingly MG induces hypertension (Wang et al., 2004) and decreases wound healing (Berlanga et al., 2005), whereas carnosine has been reported to ameliorate both these processes (Nagai et al., 1986; Quinn et al., 1992; Nijjima et al., 2002). Carnosine can also selectively kill transformed cells in culture (Holliday and McFarland, 2000) therefore any hormetic increase in its synthesis could help explain the improved cancer resistance observed when DR is imposed (Spindler, 2005).

Synthesis of another anti-glycating agent, spermine, may be stimulated following stress because ornithine decarboxylase (ODC), the first enzyme in the pathway of polyamine synthesis, is reported to be upregulated under oxidative stress and UVB irradiation (Gugliucci, 2005), conditions known to provoke glycoxidation phenomena. Gugliucci (2005) also suggests that the greatly increased ODC levels that are seen early in diabetic rat kidney may be a glycation-inhibiting response in this tissue. Such behaviour is consistent with the present proposal that anti-glycating mechanisms are subject to hormetic activation during brief periods of glycolysis. It may not be coincidental that ODC has relatively short half-life, which may permit rapid adjustment to cellular polyamine levels.

Bassi et al. (2005) have recently shown that macrophages can undergo an adaptive response when exposed to glycated serum. In particular, exposure to a sub-toxic amount of AGE (5%) increased anti-oxidant activity and provided protection against subsequent treatment with 10% AGE, while 10% AGE was lethal to non-adapted cells. These observations are consistent with the suggestion that responses to glycation may also be hormetic.

6. Testing these proposals

In order to test the validity of the above proposals it would be necessary to monitor the RQ of animals fed every other day when not calorically restricted to show any association between longevity and suppression of glycolysis. Manipulation of the anti-MG defences could reveal whether MG plays any causative role in development of the aged phenotype. For example would inhibition of glyoxalase or deficiency in carnosine, polyamine or pyridoxamine levels suppress the
beneficial effects of DR? Conversely would up-regulation of anti-MG defences suppress the deleterious effects of ad libitum feeding? Measurement of the anti-MG agents in DR animals immediately after feeding should reveal if any hormetic effects are induced.

7. Glycolysis and mechanisms of ageing

The proposals made here suggest that the source of age-related cellular dysfunction under certain circumstances may not be ROS originating entirely within mitochondria. It can be argued that active functional mitochondria suppress ageing because aerobic ATP generation decreases the requirement for glycolytically derived ATP and therefore suppresses glycolysis. When mitochondria become dysfunctional, however, MG generation is increased because glycolysis increases to compensate for the lessened amount of aerobically derived ATP. As discussed above, ROS generated extra-mitochondrially by MG and glycated polypeptides can damage the mitochondrial membranes, including the permeability transition pore, to produce features characteristic of senescence. Persistent glycolysis could provide a continuous source of mitochondrial damage and ROS generation in ad libitum-fed animals, whereas DR would suppress glycolytically generated glycation agents such as MG and thereby decrease the occurrence of macromolecular damage. Additionally, occasional glycolysis during feeding in DR animals may be hormetic by upregulating anti-glycating activities.

Masoro (2005) and Walker et al. (2005) point out that DR is accompanied by an increase in oxygen consumption, when ageing and deleterious oxidative events are suppressed. If excess glycolytic intermediates and/or their by-products are at least partly responsible for senescence in ad libitum-fed animals, the apparent paradox that ageing can be delayed when oxygen usage is increased during DR can be explained.

It seems reasonable to suggest, due to the multifactorial nature of ageing, that any process such as DR which clearly influences the onset of time-dependent cellular dysfunction would operate via a variety of mechanisms. The present proposals on the possible metabolic causes of DR-mediated suppression of ageing do not exclude the operation of any other mechanism(s). Indeed it would be unreasonable to assume that onset of senescence in different tissues and cells is controlled by a single, universal, mechanism. For example mitochondria are thought to be central to ageing, but age-related mitochondrial dysfunction may arise via a variety of routes, such as extra-mitochondrial ROS and AGE generators, intra-mitochondrial ROS, and a decline in synthesis of the nuclear coded intra-mitochondrial proteases such as LON (Bota et al., 2002) which degrades oxidatively damaged proteins. Intrinsic mitochondrial DNA instability, due partly to poor repair, provides another possible source of age-related mitochondrial dysfunction and increased erroneous repair of mitochondrial DNA can accelerate ageing in mice (Trifunovic et al., 2004). Parenthetically, it would be interesting to determine whether other agents that alter the error rates of mitochondrial gene expression also play a role in normal ageing. For example Holbrook and Menninger (2002) showed that erythromycin treatment, which increases translational accuracy, increased lifespan in yeast. Given that much of the mitochondrial genome codes for components of the mitochondrial protein biosynthetic apparatus (mitochondrial ribosomal- and transfer-RNAs) there is a high probability that alteration to mitochondrial DNA would be deleterious towards protein biosynthesis generally in the organelle. This is in fact seen in many of the inherited mitochondrial-opathies (Taylor and Turnbull, 2005), including diabetes (Janssen et al., 1999), where mitochondrial tRNA genes are altered and thereby increase biosynthetic errors (Janssen et al., 1999) possible by failure to undergo a specific modification at the wobble position (Kirino et al., 2005). Given the high mutation rate of mitochondrial DNA, and that the predictions of the error-catastrophe theory (Orgel, 1963) were only ever tested on cytoplasmically synthesized proteins and not on those produced by mitochondrial ribosomes (Hipkiss, 2003), are we correct to disregard the error-catastrophe theory? Furthermore, the recently reported increase in replication errors in the mitochondrial DNA caused by imbalances of the organelle’s deoxyribonucleotide (dNTP) pool (Song et al., 2005), suggests a tenuous link between DR, metabolism and control of age-related mitochondrial dysfunction. It is not implausible that DR could provoke changes in dNTP precursor availability and thereby affect synthesis of the four dNTP differentially, particularly as the ratios of the four dNTPs in mitochondria seemingly varies between tissues (Song et al., 2005).

The possible effects of glycolysis on ageing-related cellular biochemistry outlined here may overlap or supplement other possible mechanisms of DR’s effects on ageing. Exogenous insulin can reverse the effects of DR on mitochondria (Lambert et al., 2004), in part because of increased glycolysis and suppressed proteolysis. Defects in insulin, insulin-like growth factors, their receptors and signalling pathways could also inhibit MG production by suppressing glycolysis, as well as negating the inhibitory effects of the hormone on intracellular proteolysis of oxidised proteins, clearly may contribute to delaying onset of the aged phenotype. Many studies have revealed a relationship between DR and the activity of histone (protein) deacetylating enzymes and in particular the interaction of DR-induced changes in gene expression with energy metabolism (see Bordone and Guarente, 2005 for recent review). Presumably in DR animals the absence of food during fasting provides the stimulus for deacetylation of acetylated protein simply to provide additional energy via mitochondrial oxidation of the released acetyl groups as well as profoundly affecting gene expression.

8. Conclusion

The mechanisms by which DR mediates its protective effects towards ageing and related pathologies may be due, at least in part, to infrequent glycolysis rather than any direct change in mitochondrial function. It is suggested that most glycolytic intermediates, especially the spontaneous by-product MG, can provoke many of the biochemical and
subcellular change normally associated with ageing and related pathologies, including mitochondrial dysfunction. While persistent glycolysis may be deleterious in ad libitum-fed animals, occasional glycolysis could be hormetic during DR and protective activities (e.g. synthesis of glyoxalase, carnosine, spermine and other agents as yet unidentified) may be specifically induced.

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References


