Available online at www.sciencedirect.com
SCIENCE DIRECT
Mechanisms of Ageing and Development 127 (2006) 8–15
mechanisms of ageing and development
www.elsevier.com/locate/mechagedev

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

Received 21 June 2005; received in revised form 6 September 2005; accepted 13 September 2005
Available online 7 November 2005

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.

Keywords: Ageing; Calories; Diet; Glycolysis; Dihydroxyacetone; Methylglyoxal; Carnosine; Spermine; Polyamines; Pyridoxamine; Glyoxalase; Hormesis; Glycation

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.

0047-6374/$ – see front matter
doi:10.1016/j.mad.2005.09.006

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 is the aldehyde 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 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 (Hipkiss and Chana, 1998; Ahmed et al., 2005b; 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 note-worthy that GAPDH is particularly susceptible to glycation by its substrates glyceraldehyde- and dihydroxyacetone-phosphates (Morgan et al., 2002).