

The human erythrocyte can become both a metabolic “Achilles’ Heel” and a “Trojan Horse”: Likely consequences of persistent excessive glycolysis

Alan R Hipkiss*

Aston Research Centre for Healthy Ageing (ARCHA), Aston University, Birmingham, B4 7ET, UK

Glycolysis and aging

There is convincing evidence that the glycolytic pathway whereby glucose is broken down to pyruvic acid and which occurs in most cells in the human body, is not necessarily a benign process. Much research has highlighted the deleterious effects of excessive glycolysis towards aging and lifespan [1-3], and the converse beneficial outcomes when glycolysis is partially suppressed [4-6]. The anti-aging effects of the mTOR inhibitor rapamycin can be explained, at least in part, by the fact that down-regulation of mTOR suppresses glycolysis and enhances mitogenesis and mitochondrial ATP synthesis, whilst upregulation of mTOR accelerates glycolysis [7-10]. This is because not only can glucose react non-enzymically with proteins to create advanced glycation end-products (AGEs), but a number of the glycolytic intermediates are more reactive than glucose. The triose-phosphates, dihydroxyacetone-phosphate (DHAP) and glyceraldehyde-3-phosphate (G3P), and their highly reactive decomposition product, methylglyoxal (MG), can all provoke synthesis of AGE (also called glycotoxins), following reaction with intracellular and extracellular proteins, nucleic acids and amino-lipids [11-13]. Indeed, number of recent reviews and perspective pieces [14-16] have emphasized the role of dietary and endogenously generated glycotoxins inducing age-associated, deleterious effects throughout the body.

Furthermore, it is important to be note that dietary glycemic index (GI) can markedly influence endogenous glycotxin generation [16,17]. A study in mice [16] in which animals were fed iso-caloric diets, but of either low GI or high GI (similar to that of the so-called modern western diet), has revealed substantial differences in MG-mediated protein modification in the animals’ eyes, liver, kidney, heart, and brain [16], as well as compromised proteostasis [17]. These findings clearly demonstrated that the rate and frequency of glycolysis (glycolytic flux) strongly influences MG-mediated macromolecular modification. Cumulatively, the above findings demonstrate that excessive glycolysis is essentially deleterious with respect to age-related dysfunction.

Glycolysis in erythrocytes

While much has been written about glucose-mediated glycation of haemoglobin in erythrocytes, it is also possible that the human erythrocyte could be a source of systemic glycation throughout the body. As erythrocytes lose their mitochondria during erythropoiesis, glycolysis is the sole energy source within the red cell. This raises the possibility that if DHAP and G3P are not immediately metabolised, their decomposition product, MG, would be generated and formation of AGEs (i.e., glycotoxins) would occur. It is suggested that under

the following circumstances this would be a likely outcome. It is possible that excessive glycolysis in humans can progressively suppress one particular step in the glycolytic pathway in erythrocytes, the consequence of which would be to increase intra-erythrocyte MG generation [18]. The glycolytic enzyme involved is triose-phosphate isomerase (TPI), which catalyses the conversion of DHAP to G3P. Studies, initially made nearly 30 years ago [19,20], showed that TPI is not a true catalyst because the enzyme’s structure can become altered as a result of its catalytic activity: research showed that two asparagine residues (15 and 71) in TPI can undergo spontaneous deamidation as a consequence of its catalytic action, this has been termed [20] “molecular wear and tear”. One consequence of this is the dissociation of TPI into monomers and loss of enzymatic activity due to their subsequent proteolysis. Furthermore, it has been stated by two eminent experts in protein deamidation [21] that “the probability of deamidation of an individual TPI molecule is a function of the number of times it is used as a catalyst”. Thus, excessive TPI-mediated catalysis can result in a decline in enzyme activity, especially in human erythrocytes where synthesis of replacement protein is impossible. Consequently, in human erythrocytes, it is possible that under such circumstances TPI may become rate limiting causing DHAP accumulation; not only is DHAP a glycating agent but its spontaneous decomposition product, MG, is a well-recognised source of much age-related macromolecular modification and AGE (glycotxin) generation [3]. Interestingly, human erythrocytes possess at least 4-times more TPI than any other glycolytic enzyme [22], which is indicative of an evolutionary adaptation presumably to prevent TPI insufficiency during the limited red cell life-span. However, it is reasonable to suppose that during the majority of human evolution, the hunter-gatherer diet would have contained very much lower amounts of carbohydrate than that of the contemporary western diet. Consequently, the in-built 4-fold excess of TPI in the human erythrocyte may be insufficient to cope with the modern high-GI western diet. Thus, it is suggested that the human red blood cell, whose membrane is permeable to MG, when presented with an almost continuous high-GI diet, may be a systemic source of MG,

*Correspondence to: Alan R Hipkiss, Aston Research Centre for Healthy Ageing (ARCHA), Aston University, Birmingham, B4 7ET, UK, E-mail: alanandjill@lineone.net

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transporting the glycating agent throughout the body and thereby generating glycotoxins in a variety of tissues and accelerating age-related changes and dysfunction. It might be anticipated that the erythrocytic glyoxalase system would dispose of any MG generated within the red cells, but it has been shown that glyoxalase-1 activity declines during erythrocyte maturation [23], an observation further suggesting that over-production of MG in red cells is potentially problematic.

It is interesting to note that (i) high GI diets are associated with amyloid accumulation in the brain (as occurs in neurodegenerative disease) [24] and (ii) erythrocytes contain alpha-synuclein [25], a protein which is not only highly prone to MG-induced glycation [26] but which is also a component of Lewy bodies, whose accumulation is strongly associated with age-related dementia, Alzheimer’s disease and Parkinson’s disease [27]. Thus, it is possible that excessive and persistent glycolysis in human erythrocytes would not only increase alpha-synuclein glycation but also contribute towards the development of Lewy-bodies and neurodegenerative disorders by providing a systemic source of glycated alpha-synuclein, especially should MG-induced red cell lysis (eryptosis) occur [28]. That alpha-synuclein might possess prion-like properties [29] simply adds to the problem.

Conclusions

In summary, one can safely state that highly glycated proteins (AGEs or glycotoxins) can profoundly influence aging onset. However, not only can glycotoxins be generated by heating food, but they can also be generated endogenously via excessive and persistent glycolysis. Consequently, it is suggested that excessive glycolysis in human red cells can potentially provide a systemic source of MG and glycated alpha-synuclein, and under such circumstances, the human erythrocyte may be regarded as not only as a metabolic “Achilles’ Heel” but also a “Trojan Horse.”

Conflict of interest

There is no conflict of interest.

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