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Journal of Nutrition & Food Sciences

Short Communication

On Carnosine, Glucose Metabolism, Erythrocytes, Cell Senescence, Covid-19 and Human Health-Span

Alan R Hipkiss*

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

The recent paper by Kingsley *et al.* [1] highlighted the potential role of the microbiome, when exposed to high glucose diets, as a source of glycotoxins, not only in a model organism (the nematode *Caenorhabditis elegans*) but also in humans. The authors demonstrated that exposure of *Escherichia coli* (the food source of C. elegans) to high glucose diets resulted in enhanced methylglyoxal (MG) generation and consequent accumulation of advanced glycation end-products (AGEs i.e. glycotoxins). Kingsley *et al*. also showed that the dipeptide carnosine not only seemed to prevent glycotoxin accumulation but also had beneficial effects on organism health-span and lifespan. It is interesting to note that some 20 years ago that carnosine was shown to delay senescence in cultured human fibroblasts cultured in the presence of glucose [2].

Human erythrocytes have recently been shown [3] to contain carnosine, presumably synthesized during erythropoiesis. Not only are human erythrocytes solely glycolytic but they are readily exposed to glucose, following the sugar's transport from the digestive tract to the blood. Notwithstanding the likely effects of the microbiome in the human gut (analogous to the presence of *E. coli* in the *C. elegans* gut), it is possible that, when presented with persistently raised glucose levels, erythrocytes provide a potential and additional source of MG. This is because the glycolytic enzyme triosephosphate isomerase (TPI) is not a true catalyst because its primary structure can become altered as a consequence of its catalytic activity. Discovered about three decades by Gracy and co-workers [4], it was shown that certain asparagine residues (numbers 15 and 71) in TPI undergo spontaneous deamidation as a consequence of enzyme's catalytic activity. It has been concluded that "the probability of deamidation of an individual TPI molecule is a function of the number of times it is used as a catalyst" [5]. The resultant deamidated protein dis-associates into monomers which are subject to proteolytic attack by intracellular proteases [6]. Should TPI activity become a rate-limiting step in glycolysis, its substrate, dihydroxyacetone phosphate (DHAP), would accumulate [7]. Not only is DHAP a glycating agent but it spontaneously decomposes into the even more reactive MG. That TPI protein levels are very much higher than any other glycolysis enzyme in human erythrocytes [8] suggests an evolutionary adaptation to compensate for the likely decline in TPI activity during the 3-4 month lifespan of human red cells. However it is likely that the current "Western" diet contains far more carbohydrate than that of humans during the millions of years of their evolution. Consequently it is likely that TPI may become rate-limiting in the erythrocytes of modern humans chronically consuming excessive quantities of glucose (as evidenced by increased obesity in many "western" societies), thereby causing MG accumulation, despite the presence of both carnosine and glyoxalase activity which should prevent glycation and its deleterious consequences. It is interesting to note that erythrocyte glyoxalase activity declines with red cell age [9], and that erythrocyte carnosine levels decline with donor age [3]. Other studies have shown that blood levels of carnosine are very much lower in individuals suffering from age-related macular degeneration [10] and that low levels of serum acetyl-carnosine (which is resistant to serum carnosine activity) are strongly associated with frailty in humans [11].

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

Received Date: April 04, 2021

Accepted Date: May 21, 2021

Published Date: May 27, 2021

Citation: Hipkiss AR (2021) On Carnosine, Glucose Metabolism, Erythrocytes, Cell Senescence, Covid-19 and Human Health-Span. J Nutr Food Sci 4: 030.

Recent studies have shown that carnosine can facilitate macrophage-mediated clearance of senescent cells [12] and that cellular senescence may be a mediator covid-19 pathogenesis [13], observations which reinforce the suggestion [14-16] that the anti-inflammatory dipeptide, carnosine, should be explored for its potential towards controlling covid-19 infection etc.

It is concluded that (i) in addition to the microbiome, human erythrocytes when over-supplied with glucose are also a potential source of glycating agents such as methylglyoxal, and (ii) erythrocyte carnosine and serum N-acetyl-carnosine may provide protection against endogenously generated methylglyoxal, thereby possibly enhancing human health.

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