Short Communication

Analysis of the Role of Vitamin C Synthesis Loss in Primates’ Evolution; Solving an Evolutionary Puzzle

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Abstract

Vitamin C is a water-soluble compound with anti-oxidant properties that is essential for collagen synthesis and protection of living organisms against oxidative stress. These important roles, and the relatively large amounts of vitamin C required daily, likely explain why most vertebrate species are able to synthesize it but surprisingly; many species of anthropoid primates, guinea pigs, as well as some bats have lost the capacity to synthesize it. We hypothesized that the loss of vitamin C synthesis in early primate ancestors contributed to their relatively long life spans through up-regulation of hypoxia induced factor 1α (HIF1α), a transcription factor that plays an essential role in cellular response to oxidative stress.

Key words: Ascorbic Acid; Oxidative Stress; Primates; HIF1alpha protein, Xenopus, Longevity

Introduction

Vitamin C or ascorbate is an essential nutrient for humans and certain other animal species. It is a cofactor in many different enzymatic reactions, the most important of which is collagen synthesis [1]. It also functions as a reducing agent and oxygen radical scavenger [2]. Most animals and plants have the ability to synthesize vitamin C by converting monosaccharides – most likely glucose- to ascorbate [3]. Plants, accomplish this by using mannose or galactose [4], while some animals rely on glucose [3]. The first step of Vitamin C synthesis is the formation of UDP-glucuronic acid which undergoes a series of enzymatic reactions until it forms L-gulonolactone which reacts with oxygen to form ascorbic acid [3]. This last step is catalyzed by L-gulonolactone oxidase an enzyme that is deficient in humans and other primates due to the accumulation of several mutations that turned it into a pseudogene [3].

Among the animals that have lost the ability to synthesize vitamin C are simians and tarsiers, which together make up one of two major primate suborders, Haplorrhini [5]. This group includes humans. The other more primitive primates (Strepsirrhini) retained the ability to synthesize vitamin C. Members of the rodent family Caviidae which includes guinea pigs and capybaras also lost the ability to synthesize vitamin C [3, 6]. All species that do not synthesize vitamin C require it in the diet like fruits and vegetables [7]. In humans Deficiency in this vitamin causes scurvy; a disease characterized by recurrent bleeding from gums and mucus membranes, suppurating wounds, loss of teeth and, eventually, death [8].

The causes of vitamin C synthesis loss in humans and other species have not yet been satisfactorily explained. How can synthesis of something so crucial for survival be eliminated by natural selection? The answer to this question can be partially explained by the notion that our early ancestors - like their descendants today- relied heavily on diets rich in vitamin C [9]. Without the constraints of natural selection to maintain the integrity of genes involved in the pathway of vitamin C synthesis, the pathway will ultimately disintegrate and genes will accumulate several mutations turning into pseudogenes; a more disordered state according to the second law of thermodynamics. The same thing happened for the case of eta globin gene [10]. If however we assumed that the first mutations that occurred in our early ancestors bore no fitness benefit (i.e. both the animals with two
We proposed a theory that loss of vitamin C synthesis in early primates had a survival benefit; it led to the extension of cell life response to hypoxia outweighs the risk of developing scurvy. Professor Li et al. [14] have demonstrated that vitamin C up-regulates a transcription factor called Hypoxia Inducible Factor 1α (HIF1α) [12], which is responsible for activation of hundreds of stress-related genes [13]. Grano and De Tullio (2007) proposed that loss of vitamin C synthesis can finely regulate HIF1α activation on the basis of the dietary intake of vitamin C [14]. This theory overlooks the benefits of HIF1α titration system, and even if it doesn’t, it is difficult to understand that the benefit of fine tuning of cellular synthesis can finely regulate HIF1α activation on the basis of the dietary intake of vitamin C [14]. This theory overlooks the benefits of HIF1α titration system, and even if it doesn’t, it is difficult to understand that the benefit of fine tuning of cellular synthesis can finely regulate HIF1α activation on the basis of the dietary intake of vitamin C [14].

More recently Grano and De Tullio, (2007) proposed another hypothesis, based on the studies by Knowles et al, (2003) who demonstrated that vitamin C up-regulates a transcription factor called Hypoxia Inducible Factor 1α (HIF1α) [12], which is responsible for activation of hundreds of stress-related genes [13]. Grano and De Tullio (2007) proposed that loss of vitamin C synthesis can finely regulate HIF1α activation on the basis of the dietary intake of vitamin C [14]. This theory overlooks the benefits of HIF1α titration system, and even if it doesn’t, it is difficult to understand that the benefit of fine tuning of cellular response to hypoxia outweighs the risk of developing scurvy.

We proposed a theory that loss of vitamin C synthesis in early primates had a survival benefit; it led to the extension of their life spans. Primates as a group live about twice as long as expected for a mammal of the same body size [15], and the cause of their longevity has not yet been fully elucidated. We suggested that the early loss of vitamin C synthesis altered the life span through a mechanism involving modulation of HIF1α. Previous researches showed that low ascorbate level is associated with overexpression of HIF1α and extension of the life span of C. elegans through many different pathways [16, 17]. In mammalian cells HIF-1-mediated transcriptional response is involved in many physiological responses related to cellular senescence and aging which include angiogenesis, vasculogenesis, axon guidance, and adaptation to hypoxia [18]. Researchers found that the ability of cells to express HIF-1 related response under hypoxic conditions declines with age [18]. These observations may explain the susceptibility of aged organisms to hypoxic stress. In human cells HIF-1 was shown to increase the activity of telomerase enzyme [19] the promoter of telomerase gene contains two HIF-1 consensus motifs and these are activated by HIF-1 as has been shown by in vitro studies [19]. Eric et al., (2007) found that hypoxic environment in cultured human lung fibroblasts extend their life span through activation of the transcription factor hypoxia-inducible factor (HIF) [20]. Together these studies suggest that oxygen limitation and/or activation of HIF-1 play important roles in cellular senescence.

Why does not exogenous dietary vitamin C prevent the downward activation of HIF that leads to lifespan extension? The answer is in epigenetics. Unlike constitutive vitamin C synthesis, dietary vitamin C is episodic and unpredictable. It is not the unavailability of vitamin C that matters; it is its unavailability at certain critical times in the animal’s life that is important. A recent study has shown that vitamin C acts as a widespread demethylating agent in the genome of human embryonic stem cells [21]. Pierre (2014) studied epigenetics in aging and found that epigenetic drift in the form of genomic methylation/demethylation correlates strongly with life span of the animal species [22].

Trials to prolong life span by vitamin C supplementation yielded conflict results, some studies suggest an increase in lifespan, other studies failed to observe any beneficial effect of vitamin C on longevity and some studies even reported a decrease in lifespan following vitamin C supplementation [23]. This is most probably due to compensatory down-regulation of other antioxidants like superoxide dismutase [24].

Lifespan of animals is determined by complex interactions between genetics and environment. Reducing these factors to a single gene or a single factor is preposterous. In the early days of primates’ ancestors (following the extinction of dinosaurs) there were probably few predators, and living examples reveal that animals with few natural predators live relatively longer [25]. This, combined with other factors like loss of vitamin C synthesis may have contributed to the relatively longer life span of primates. Primates as a group live about twice as long as expected for a mammal of the same body size, and humans live at least twice as long as expected for a primate of their body size [15]. We have noted that other groups of animals who also lost the ability to synthesise vitamin C like bats and guinea pigs live relatively longer than other animals with the same size and weight [26, 27].
We are not concluding that the extended life span seen in these animal groups is due to loss of vitamin C synthesis only; it would be an example of an aberrant reductionism but it worth to be considered.

Conclusion

Longer life spans extend the reproductive age of animals, increasing the number of offspring, delays the maturation time and allows for larger brain development, all are characteristics of primates. The loss of vitamin C synthesis in early primates may have contributed to the emergence of these characteristics.

References


