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Review

Birds and longevity: Does flight driven aerobicity provide an oxidative sink?

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ABSTRACT

Birds generally age slower and live longer than similar sized mammals. For birds this occurs despite elevated blood glucose levels that for mammals would in part define them as diabetic. However these data were acquired in respiration states that have little resemblance to conditions in healthy tissues and mitochondrial RS production is probably minimal in healthy animals. Indeed mitochondria probably act as net consumers rather than producers of RS. Here we propose that (1) if mitochondria are antioxidant systems, the greater mitochondrial mass in athletic species, such as birds, is advantageous as it should provide a substantial sink for RS. (2) The intense drive for aerobic performance and decreased body density to facilitate flight may explain the relative insensitivity of birds to insulin, as well as depressed insulin levels and apparent sensitization to glucagon. Glucagon also associates with the sirtuin protein family, most of which are associated with caloric restriction regulated pathways, mitochondrial biogenesis and life span extension. (3) We note that telomeres, which appear to be unusually long in birds, bind Sirtuins 2 and 4 and therefore may stabilize and protect nuclear DNA. Ultimately these flight driven responses may suppress somatic growth and protect DNA from oxidative damage that would otherwise lead to ageing and non-viral cancers.

1. Introduction

Increasing human life quality in developed nations will prove to be one of humanity's greatest challenges. While mean lifespan in the EU and USA is 78 years and increasing by ~2 years per decade, indices of human life quality are not following suit (Andreyev et al., 2005; Brown, 2008). As the average onset of degenerative diseases appears to be fixed, e.g. Alzheimer's (73 years), Parkinson's (60–65 years), arthritis (47 years) and senescence-age related cancers (77% of cancers occur over 50 years of age) (Brown, 2008), a future world filled with incapacitated elderly is eminent (the %population >65 years in the USA = 4.1% in 1900; 12.6% in 2000, projected to 20% by 2030 (Gavrilov and Heuveline, 2003)). Effectively humans are living longer, yet the onset of age related diseases remain fixed.

If ageing is considered a disease brought about by specific processes it maybe treatable, if not curable (reviewed by Lane, 2005). However, to study ageing we need appropriate model systems. Rodents provide useful diseased or broken state models, as they age rapidly and can be manipulated. Yet the "fixed" long living state is rarely considered, and such models are necessary to attempt to study successful anti-ageing processes.

Maximal longevity appears to scale allometrically (i.e. larger animals live longer), as does mass specific metabolic rate (Hulbert and Else, 2000). According to this relationship, humans qualify as a longer-lived species as, relative to body mass, humans should only live for 27 years (Ricklefs et al., 1996), yet the oldest verified human, Jeanne Calmont, lived for 122 years. Bowfin whales (*Balaena mysticetus*) live for ~103 years (dated from harpoon remnants, George et al., 1999). Yet for a 50 tonne animal this is unremarkable, as allometric relationships predict ~100 years (Ricklefs et al., 1996). In other lineages of mammals studied, the ~30–35 g naked mole rat (*Heterocephalus glaber*) lives an exceptional >28 years (Buffenstein and Jarvis, 2002), and numerous bats defy longevity expectations relative to their body mass.

Abbreviations: CR, caloric restriction; DCA, dichloroacetic acid; ETF, electron transfer flavoprotein; ETS, electron transport system; FOXO1, Forkhead box protein O1; H_2O_2, hydrogen peroxide; Gp, DHglycerol 3-phosphate dehydrogenase; IGF-1R, insulin-like-growth factor receptor 1; IR, Insulin Receptor; MR, metabolic rate; OH, hydroxyl radical; PGC, peroxisome proliferator-activated receptor-γ coactivator-1α; O_2, -superoxide; O, singlet oxygen; Pol-G, DNA Polymerase Gamma subunit; RS, reactive species; Sirt, sirtuin protein; SOD, Super Oxide Dismutase; UCP, uncoupling protein.

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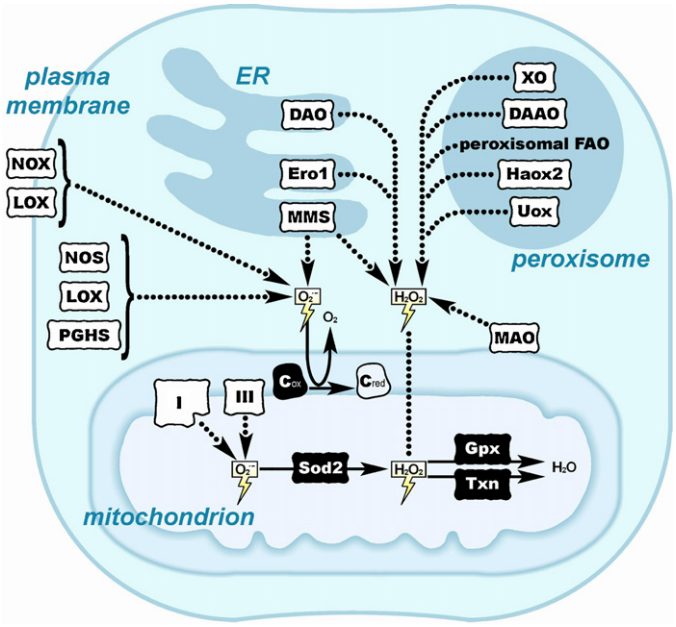

Fig. 1. Reactive species (RS) production and consumption. While not all the potential sources are illustrated many sources of RS occur externally to the mitochondrion and these most likely exceed the production capacities of Complexes I and III. The mitochondria contain numerous mechanisms by which it can dispose of RS one of which (cytochrome *c*) is coupled to ATP synthesis. Abbreviations: Cox, oxidized cytochrome *c*; Cred, reduced cytochrome *c*; DAAO, D-amino acid oxidase; DAO, diamine oxidase; Ero1, Endoplasmic oxidoreductin-1; FAO, fatty acid oxidase; Haox2, L-2-hydroxyacid oxidase; I and III, electron transport system complexes I and III; IM, inner mitochondrial membrane; IMS, intermembrane space; LOX, lipoxygenases; MAO, mono amine oxidase; MMS, microsomal monooxygenase system (cytochromes P450 and cytochrome b5); NOS, NO synthase; OM, outer mitochondrial membrane; PGHS, PGH synthase; Sod2, mitochondrial Cu/Zn superoxide dismutase; Txn, Thioredoxins; Uox, urate oxidase; XO, xanthine oxidase; GPX, glutathione peroxidase; NOX, NADPH oxidases.

As a phylogenetic lineage, birds remarkably defy ageing, and live relatively and absolutely much longer than most mammals. Anectodal claims suggest Sulphur Crested Cockatoos (*Cacatua galerita*) reach 120–142 years (validated data suggest 57 years, Brouwer et al., 2000). "King Tut", a Salmon Crested Cockatoo (*C. moluccensis*) was age validated to at least 69 years (Brouwer et al., 2000). Seabirds, such as gannets and albatrosses, can reach 30–60 years (Ismar et al., 2010; Tickell, 2000). While the maximum recorded lifespan of a 20 g house mouse (*Mus musculus*) is only 4 years (Holmes et al., 2001), the tiny 5 g Broad-billed Hummingbird (*Selasphorus platycercus*) can live for 14 years (Holmes and Austad, 1995). Zoo records and wild tagging data can in part account for confounding reductions of predation through flight (Ricklefs, 1998), but even for the "short-lived species", most birds still live longer than mammals of equivalent body mass (e.g. hens Gallus gallus 20 years, quail Coturnix spp. 6–7 years, Holmes and Austad, 1995). Reproductive output in birds and particularly amongst seabirds (Brouwer et al., 2000; Holmes and Ottinger, 2003), also appears to be exceptional (Brouwer et al., 2000; Holmes and Ottinger, 2003: although not universal (Low et al., 2007), many avian species maintain consistent reproductive effort until death without patterns of breeding senescence (Keller et al., 2008).

What factors might underlie the ability of birds to live long and healthy lives? A striking feature of birds is that they are extremely athletic given that most species (>99%) fly. Birds attain high respiratory efficiencies due to flow-through counter-current pulmonary systems, and their metabolic rates (MRs) and estimated lifetime energy expenditures are 2.5–15 fold greater than that of similar-sized mammals (Harr, 2002). Birds also maintain body temperatures up to 5 °C higher than most mammals. Finally and perhaps most remarkably, most birds maintain blood glucose levels 1.5–2 fold that of mammals (Braun and Sweazea, 2008); yet even in the face of oxidative stressors they appear to avoid complications associated with diabetes (Hilton et al., 2010; Holmes et al., 2001), and in contrast with mammals they can even regenerate neuronal tissues (Woolley and Rubel, 2002).

While birds still do accrue age related pathologies, the onset is delayed relative to mammals (Holmes and Martin, 2009; Holmes and Austad, 1995; Holmes and Ottinger, 2003), and birds may also accrue cancers at only 40% the rate of mammals (Effron et al., 1977; Fox, 1912; Galis, 1999; Lombard and Witte, 1959). The differences between birds and mammals may thus hold clues to the physiological mechanisms that suppress ageing and age-related pathologies.

1.1. Longevity and ageing

For birds and bats (please see discussion on bats in Section 1.7 below), flight clearly provides protection from physical and biotic causes of mortality (Wasser and Sherman, 2009), just as chemical defenses of toxic fishes, amphibians, and reptiles increases body size dependent lifespans (Blancoa and Sherman, 2005). Although this provides a behavioral mechanism and life history strategy of reduced predation and increased longevity, how the physiological/molecular ageing processes of age are delayed or diminished in birds is yet to be resolved.

It is well known that cell viability declines with age due to accumulated genetic mutations in nuclear and mitochondrial genomes, accumulation of un-degradable products, and progressive shortening of telomeres that disrupt cell division, function and genomic stability. Disruption of DNA also impacts mitochondrial genomes and therefore efficient bioenergetic supply from mitochondria (Partridge and Gems, 2002) and further promotes senescence, programmed cell death (apoptosis), and autophagy. While these processes suppress tumours (Finkel et al., 2007), for some tissues (e.g., mammalian heart and brain) loss of cells leads to organ failure and death (Finkel et al., 2007).

Pearl first proposed the "rate of living" limited lifespan, due to the general phenomenon that small animals generally age faster and have high MRs (Pearl, 1928). Indeed, some ectotherms with extremely low MRs live extremely long (tortoises ~150 years, quahog clam ~200 years). However, the rate of living hypothesis is confounded as birds and bats have extremely high MRs and lifetime energetic expenditures, and are long lived for their adult masses and in absolute terms (Holmes and Austad, 1995; Holmes and Ottinger, 2003).

Other explanations for differences in longevity have been proposed, these range from differences in telomere dynamics and lengths, oxidative stress management, hormonal and genetic capacities, membrane composition and immune function. In the context of birds we propose that there are three interdependent mechanisms that may account for avian longevity:

(1) Currently it is thought that birds release less mitochondrial derived free radicals or reactive species (RS). Some more recent views are discussed and we contend that mitochondria may in fact be consumers of RS in vivo, not RS producers.
(2) Hyperglycemia provides insight to mechanisms that extend the lifespans of birds. Most birds studied show a clear depression of the insulin axis and enhancement of the glucagon axis. The insulin axis promotes growth, glycogen synthesis and cancers. Glucagon promotes catabolism and aerobicity through pathways mostly associated with calorie restriction, which itself mediates the extension of lifespan.