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Regulation of longevity and oxidative stress by nutritional interventions: Role of methionine restriction

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ABSTRACT

Comparative studies indicate that long-lived mammals have low rates of mitochondrial reactive oxygen species production (mtROSp) and oxidative damage in their mitochondrial DNA (mtDNA). Dietary restriction (DR), around 40%, extends the mean and maximum life span of a wide range of species and lowers mtROSp and oxidative damage to mtDNA, which supports the mitochondrial free radical theory of aging (MFRTA). Regarding the dietary factor responsible for the life extension effect of DR, neither carbohydrate nor lipid restriction seems to modify maximum longevity. However protein restriction (PR) and methionine restriction (at least 80% MetR) increase maximum lifespan in rats and mice. Interestingly, only 7 weeks of 40% PR (at least in liver) or 40% MetR (in all the studied organs, heart, brain, liver or kidney) is enough to decrease mtROSp and oxidative damage to mtDNA in rats, whereas neither carbohydrate nor lipid restriction changes these parameters. In addition, old rats also conserve the capacity to respond to 7 weeks of 40% MetR with these beneficial changes. Most importantly, 40% MetR, differing from what happens during both 40% DR and 80% MetR, does not decrease growth rate and body size of rats. All the available studies suggest that the decrease in methionine ingestion that occurs during DR is responsible for part of the aging-delaying effect of this intervention likely through the decrease of mtROSp and ensuing DNA damage that it exerts. We conclude that lowering mtROS generation is a conserved mechanism, shared by long-lived species and dietary, protein, and methionine restricted animals, that decreases damage to macromolecules situated near the complex I mtROS generator, especially mtDNA. This would decrease the accumulation rate of somatic mutations in mtDNA and maybe finally also in nuclear DNA.

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1. Introduction

What are the mechanisms regulating the rate of aging? Although perhaps multi-causal, the main causal factors determining the rate of aging are expected to be relatively few (Barja, 2008) and highly conserved across closely related species like different mammals. Numerous theories of aging have been proposed (Medvedev, 1990). However, any appropriate theory should be able to explain the four main characteristics of aging (Strehler, 1962): it is progressive, endogenous, irreversible, and deleterious (for the individual). Denham Harman first proposed in 1956 that free radicals, and especially those of mitochondrial origin (Harman, 1956; Harman, 1972; Miquel et al., 1980), are among the main causes of aging. The Mitochondrial Free Radical Theory of Aging (MFRTA) is supported by different kinds of experimental and comparative studies (Barja, 2004a,b; Barja et al., 1994a; Pamplona and Barja, 2011; Pérez-Campo et al., 1998; Sohal and Weindruch, 1996). This review summarizes the available evidence concerning the MFRTA focusing in dietary models that increase maximum longevity (dietary, protein and methionine restriction), comparative studies and the underlying mechanisms involved.

2. Mitochondrial free radical theory of aging

In the absence of pathology, mitochondria are an important cellular source of reactive oxygen species (ROS) that can oxidatively damage many different kinds of cellular macromolecules including lipids, proteins and, especially in the case of aging, mitochondrial DNA (mtDNA) (Barja et al., 1994a). MFRTA fits well with the four Strehler's rules of aging: mitochondrial ROS production (mtROSp) comes from endogenous sources (the mitochondrial respiratory chain), progressively and continuously occurs throughout life, and it is finally detrimental (for the individual) in an irreversible way due to the capacity of ROS to give rise to established somatic mutations in mtDNA (Barja, 2004a,b; Barja and Herrero, 2000; Barja et al., 1994a,b; Ku et al., 1993; Sohal

Abbreviations: 8-oxodG, 8-oxo-7,8-dihydro-2′deoxyguanosine; BER, base excision repair; DR, dietary restriction; %FRL, percentage free radical leak; IGF, insulin-like growth factor; IIS, insulin/insulin-like growth factor signaling; MetR, methionine restriction; mtDNA, mitochondrial DNA; MFRTA, mitochondrial free radical theory of aging; $mtVO_2$, mitochondrial oxygen consumption; mtROSp, mitochondrial ROS production; nDNA, nuclear DNA; PR, protein restriction; SAH, S-adenosylhomocysteine; SAM, S-adenosylmethyonine.

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et al., 1990), and maybe finally also in nuclear DNA (nDNA) (Caro et al., 2010). Therefore, mtROSp seems to be one of the main factors that genetically determine the aging rate and the species-specific maximum life span potential (from here on called "longevity").

It is now well known that mtROS generation occurs not only at complex III (Boveris and Cadenas, 1975; Boveris et al., 1976) but also at complex I (Barja and Herrero, 1998; Genova et al., 2001; Herrero and Barja, 1997; Kudin et al., 2004; Kushnareva et al., 2002; Lambert and Brand, 2004). The main electron transport components that can be responsible for complex I ROS generation are the following: those located in the hydrophilic complex I domain facing the mitochondrial matrix, the flavin, and some of the FeS clusters (Genova et al., 2001; Herrero and Barja, 2000), or that situated in the inner membrane arm of complex I, the ubiquinone (Herrero and Barja, 2000; Lambert and Brand, 2004; Murphy, 2009; Treberg et al., 2011). In contrast, complex III would produce ROS directed only to the cytosolic side of the inner membrane, although recent studies suggest that part of the production could also occur towards the matrix (Brand, 2010). Oxygen derived radicals can damage all kinds of macromolecules, but mtDNA is especially important in the case of aging because the final result can be the irreversible loss or alteration of all the copies of relevant DNA-coded information of a cell, which are needed for its survival or proper functioning (Marnett and Plastaras, 2001). Determinant mechanisms of the steady-state level of oxidative mtDNA damage include its location, very close to or even in contact with the site/s of mtROS production at the inner mitochondrial membrane (Barja, 2004b; Barja et al., 1994a).

Comparative studies have shown that long-lived species have low rates of mtROSp and oxidative damage (Barja, 2004a,b; Barja and Herrero, 1998; Barja et al., 1994a,b; Herrero and Barja, 1997, 1998; Lambert et al., 2007; Sohal et al., 1994). Long-lived species produce lower amounts of ROS at their tissue mitochondria than short-lived ones, and this difference seems to occur at complex I, not at complex III. This is due in various cases to the possession of a lower percent leakage of total electron flow in the respiratory chain (%free radical leak: %FRL; Barja, 2004a). The frequently low %FRL of the mitochondria from animals with longevities higher than expected for their body size and metabolic rate means that these animals usually have mitochondria more efficient in avoiding ROS generation. In addition, they can also have (as in pigeons) a lower amount of complex I protein (Lambert et al., 2010; Pamplona et al., 2005; St-Pierre et al., 2002), and then less mtROSp. In summary, available scientific data supports a negative correlation between mtROS production and longevity in vertebrates.

In agreement with their low rates of mtROS generation, long-lived mammals have lower steady-state levels of oxidative damage (estimated by measuring 8-oxo-7,8-dihydro-2′deoxyguanosine: 8-oxodG by HPLC-EC) in their mtDNA (Barja, 2004a,b; Barja and Herrero, 2000). It is interesting to note that long-lived animals do not possess higher levels of molecules protecting from free radicals. Contrarily to this, long-lived animals have lower tissue levels of endogenous antioxidants (reviewed in Pérez-Campo et al., 1998; see also Table 1 in Pamplona and Constantini, 2011) as well as lower repair activities of endogenous DNA damage (base excision repair — BER pathway; Page and Stuart, 2011) and of protein repair through the 20S/26S proteasome (Portero-Otín et al., 2004; Salway et al., 2011) than short-lived ones. The low or very low antioxidant levels of long-lived animals, up to 15 lower in humans than in hamsters in the case of liver GSH-peroxidase (see Fig. 3 in Pérez-Campo et al., 1998), was a seminal observation that led us to propose that long-lived animals should have low rates of mtROSp and that this was the relevant trait for aging, not the antioxidant levels (Barja et al., 1994a; Ku et al., 1993; Lambert et al., 2007; López-Torres et al., 1993a; Pérez-Campo et al., 1994, 1998). Besides, many experimental studies have shown that increasing antioxidant enzymes like SOD, catalase or GSH-peroxidases in transgenic mice or in the diet does not increase animal longevity (Barja, 2004a; Muller et al., 2007; Sanz et al., 2006a) except in *Caenorhabditis elegans* (Melov et al., 2000) but only under specific conditions (Keaney and Gems, 2003). If there is a low rate of mtROS induced damage in long-lived species, there is also a smaller need for endogenous antioxidants, or for protein and DNA repair systems, which could be transitorily induced when needed to come back again to low levels when the episodic increase in oxidative stress has been overcome (Lee et al., 1996; López-Torres et al., 1993b). In this way cells save much energy which otherwise would be invested in the protein synthesis needed to continuously maintain high levels of antioxidants and DNA repair enzymes when they are not needed. Instead, long-lived species decrease mtROSp which is simpler, more efficient, and much less energetically expensive than continuously maintaining high levels of endogenous antioxidants and repair systems. On the other hand, long-lived mammals also have a low degree of fatty acid unsaturation in their cellular membranes which protects them against the deleterious process of lipid peroxidation (Naudi et al., 2011; Pamplona et al., 1996, 2002a; Pamplona and Barja, 2007).

Table 1
Summary of methionine restriction (MetR) longevity experiments in mice and rats.

Manipulation	Species	Number of animals[a]	Change in (maximum) longevity	Reference
80% MetR[b]	Fisher 344 rat	30	↑ 12%	Orentreich et al. (1993)
80% MetR[b]	Fisher 344 rat	16	↑ 44%	Richie et al. (1994)
65% MetR[c]	Mice (CB6F1)	40	↑ 10%	Miller et al. (2005)
65% MetR[c] at middle age (12 months)	Mice (CB6F1)	51	↑ 5.5%	Sun et al. (2009)

↑: increase; CB6F1 = (BALB/cJ × C57BL/6)F1.
[a] Number of different animals per dietary group in each life-long experiment.
[b] Control diet: 0.86% methionine; MetR diet: 0.17% methionine.
[c] Control diet: 0.43% methionine; MetR diet: 0.15% methionine.

The studies summarized below (Sections 3 and 4) show that dietary restriction (DR), protein restriction (PR) and methionine restriction (MetR) increase longevity and decrease mtROS generation and oxidative damage to mtDNA in rodents. Those studies connect longevity and experimental studies with the MFRTA. They offer a plausible mechanism by which both long-lived animal species and DR, PR or MetR animals can slow down the rate of aging: by decreasing mtROSp. This in turn lowers mtDNA oxidative damage and then the long-term accumulation of (irreversible) somatic mutations in mtDNA (Barja, 2004a) including point mutations, as well as deletions, and therefore generating also less mtDNA fragments. These mtDNA fragments show higher levels of 8-oxodG adducts than wild type mtDNA (Suter and Richter, 1999), and are released from mouse liver mitochondria upon opening of the mitochondrial permeability transition pore (Patrushev et al., 2004). Interestingly, these fragments are present also in nDNA, and a recent study has found that the mtDNA fragments present in nDNA increase with age in both rat liver and brain (Caro et al., 2010). Such insertions have the potential to alter the nDNA sequences. According to the "mtDNA fragments insertion inside nDNA" mechanism (Barja, 2010; Caro et al., 2010) the mitochondria would continue to be the source of the aging problem in the MFRTA but the main target would be the nucleus.

In addition to the dietary studies, it has been shown that genetic manipulations also might modulate ageing. Among others, specific mutations in the insulin/insulin-like growth factor (IGF) signalling (IIS) pathway and the target of rapamycin (TOR) pathway extend longevity in a wide range of organisms (Harrison et al., 2009; Mair and Dillin, 2008; Selman et al., 2008; Taguchi and White, 2008). These upstream nutrient signalling pathways might converge and modulate transcription factors. These changes could affect nuclear responses related to mitochondrial functions, as mitochondrial biogenesis or

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