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Research review paper

Mitochondria-targeted antioxidants and metabolic modulators as pharmacological interventions to slow ageing

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ABSTRACT

Populations in many nations today are rapidly ageing. This unprecedented demographic change represents one of the main challenges of our time. A defining property of the ageing process is a marked increase in the risk of mortality and morbidity with age. The incidence of cancer, cardiovascular and neurodegenerative diseases increases non-linearly, sometimes exponentially with age. One of the most important tasks in biogerontology is to develop interventions leading to an increase in healthy lifespan (health span), and a better understanding of basic mechanisms underlying the ageing process itself may lead to interventions able to delay or prevent many or even all age-dependent conditions. One of the putative basic mechanisms of ageing is age-dependent mitochondrial deterioration, closely associated with damage mediated by reactive oxygen species (ROS). Given the central role that mitochondria and mitochondrial dysfunction play not only in ageing but also in apoptosis, cancer, neurodegeneration and other age-related diseases there is great interest in approaches to protect mitochondria from ROS-mediated damage. In this review, we explore strategies of targeting mitochondria to reduce mitochondrial oxidative damage with the aim of preventing or delaying age-dependent decline in mitochondrial function and some of the resulting pathologies. We discuss mitochondria-targeted and -localized antioxidants (e.g.: MitoQ, SkQ, ergothioneine), mitochondrial metabolic modulators (e.g. dichloroacetic acid), and uncouplers (e.g.: uncoupling proteins, dinitrophenol) as well as some alternative future approaches for targeting compounds to the mitochondria, including advances from nanotechnology.

Contents

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1. Introduction and topics reviewed

Due predominantly to decreasing birth rates, populations in most nations today are rapidly ageing (United_Nations, 2001). This unprecedented and global demographic change represents one of the main social, scientific and economic challenges of our time. However, the same demographic change also constitutes a major opportunity for novel therapeutic developments.

A defining property of the ageing process is an increase in the risk of mortality and morbidity with age (Finch et al., 1990). The incidence of cancer, cardiovascular and neurodegenerative diseases increases non-linearly, sometimes exponentially with age (Balaban et al., 2005).

Given that population ageing is inevitable unless birth rates increase dramatically, something that is both unlikely and, on a global scale, undesirable (United Nations), one of the most important tasks in biogerontology is to develop interventions leading to an increase in healthy lifespan (health span) and possibly to compress morbidity (Houtkooper et al.; Schaffer et al., 2011). It has been suggested that targeting mechanisms underlying the ageing process itself has the potential to delay or prevent not one but many (or even all) of these age-dependent conditions (Finkel, 2005; Hayflick, 2007).

One proposed public mechanism of ageing is age-dependent mitochondrial deterioration, closely related to damage mediated by one or more of the oxygen derived species known collectively as reactive oxygen species (ROS) (Halliwell and Gutteridge, 2007; Harman, 1956, 1972a,b). Although we use the term ROS a great deal in this review, it is worth pointing out that each individual oxygen-derived species has its own set of unique chemical properties, e.g.: hydroxyl radicals are far more reactive than hydrogen peroxide (Halliwell and Gutteridge, 2007). The mitochondrial electron transport chain (ETC) links the transfer of electrons from reduced cofactors to the ultimate electron acceptor of the ETC (i.e. oxygen) with the simultaneous transport of protons from the mitochondrial matrix across the inner mitochondrial membrane and into the intermembrane space. Electron transfer proceeds in discrete steps through a series of large multi-protein complexes (Complexes I–IV) embedded into the inner mitochondrial matrix (Fig. 1a). Movement of protons out of the matrix and into the intermembrane space results in an electrochemical potential ($\Delta\Psi$) which can then be used to drive protons back into the mitochondrial matrix through the ATP synthase (Complex V), facilitating the synthesis of adenosine-5′-triphosphate (ATP). However, at various sites within the ETC, in particular on Complexes I and III, electrons may occasionally leak to oxygen, forming superoxide ($O_2^{\bullet -}$) via single electron reduction (Brand et al., 2004). Superoxide itself is not very reactive and, due to its charged character, cannot cross most biological membranes. Most superoxide is converted rapidly through spontaneous dismutation and enzyme (SOD)-catalyzed reactions to hydrogen peroxide. However, if not removed, superoxide can attack mitochondrial iron–sulfur cluster containing proteins to release ferrous (Fe^{2+}) iron which can, in turn, convert hydrogen peroxide into the highly reactive hydroxyl radical (reviewed by: Halliwell and Gutteridge, 2007). Importantly, superoxide production changes non-linearly with the membrane potential $\Delta\Psi$ (Korshunov et al., 1997; Liu, 1997). Depending on experimental conditions, isolated mitochondria convert between 0.1% and 2% of oxygen consumed into ROS (Boveris and Chance, 1973; Murphy, 2009a). While it is difficult to determine exactly how many ROS are produced *in vivo* under physiological conditions (for discussion see: Murphy, 2009a), a recently described method allowed such *in vivo* measurement in fruit flies, suggesting that ROS are indeed produced *in vivo* and that ROS production rate increases with age (Cocheme et al., 2011). Furthermore, the fact that various forms of oxidative damage are detectable *in vivo* in mitochondrial and cytosolic biomolecules confirms that ROS are indeed produced *in vivo* and that some escape detoxification and continue to damage biological macromolecules *in vivo* (Halliwell and Gutteridge, 2007). It has been argued that mitochondria, being a major source of ROS, may be particularly vulnerable to lifelong accumulation of such oxidative damage (Harman, 1972a). Given the central role that mitochondria and mitochondrial dysfunction play in apoptosis, cancer, neurodegeneration, other age-related diseases, and probably in the ageing process itself, there is great interest in strategies to protect mitochondria from ROS-mediated damage (Dai and Rabinovitch, 2009; Gruber et al., 2008; Hur et al., 2010; Murphy, 2009a,b; Murphy, 2012; Skulachev et al., 2011; Smith and Murphy, 2011; Swerdlow, 2007; Wanagat et al., 2010; Weissig et al., 2001; Yen and Klionsky, 2008).

In this review we will discuss promising strategies targeting mitochondria to reduce mitochondrial oxidative damage with the aim of preventing or delaying age-dependent decline in mitochondrial function and some of the resulting pathologies. In Section 2 we will briefly review some of the evidence supporting the therapeutic promise of mitochondria-targeted interventions. Section 3 discusses small molecule antioxidants targeted to mitochondria using lipophilic cations, one of the most well developed approaches for targeting compounds to mitochondria. Section 4 discusses a class of peptide-based antioxidants that have shown mitochondrial localization and adequate therapeutic potential. Section 5 discusses examples of naturally occurring antioxidants for which there is evidence of active import into mitochondria. Finally, Sections 6, 7 and 8 discuss alternative and future approaches for mitochondrial targeting including advances from emerging nanotechnologies.