

Metabolism, oxidative stress, and ageing

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A link between metabolism and longevity was first proposed by Rubner (Rubner, 1883). From measurements on five different mammals (guinea pigs, cats, dogs, cattle, and horses), he observed that long-lived species are bigger and spend less energy per gram of tissue mass relative to short-lived species. The assumption of such link was rooted from the idea that animals have a limited supply of energy and the quicker they utilise it, the sooner they will die. This idea later became a principle of the rate of living theory (ROL, (Pearl, 1928). The oxidative stress theory suggested that the generation of free radicals is positively correlated with rate of O₂ consumption (metabolic rate), and that damage caused by these radicals accumulates with age, hence causing cell death (Harman, 1956; John R Speakman & Selman, 2011). Many studies performed on birds are consistent with this idea (Alonso-Alvarez et al., 2004; De Block & Stoks, 2008; Wiersma & Verhulst, 2005). However, the experiments performed on mammals demonstrated that the relationship between metabolic rate and mitochondrial ROS production is not straightforward (Barja & Herrero, 2000; Judge et al., 2005; Sanz et al., 2005; Selman et al., 2008; Venditti, Masullo, & Meo, 1999; Wiersma, Selman, Speakman, & Verhulst, 2004).

Most free radicals are produced in mitochondria during the oxidative phosphorylation process. However, production of such radicals was found to be driven by the mitochondrial inner membrane potential gradient ((Brand, 2000). The higher the metabolic rate is, the lower the inner potential membrane gradient would be. A lower membrane potential can also be induced directly by activation of uncoupling proteins and other mitochondrial proteins (e.g. adenine nucleotide translocate); enabling protons to be transported back to the mitochondrial matrix

without ATP being produced (John R Speakman & Garratt, 2013). In line with this model, previous research on mice, and Glanville fritillary butterflies (*Melitaea cinxia*) revealed that individuals with higher metabolic rates, corrected for body mass, had a longer life span due to activation of uncoupling proteins (Niitepõld & Hanski, 2013; Wiersma et al., 2004). Similar findings were also reported in mice in which the activation of uncoupling proteins by both chemical and genetic approaches, caused higher metabolic rates and increased longevity (Caldeira da Silva et al., 2008; Keipert et al., 2011). Many other studies on different species have also shown that life span was positively correlated with resting metabolic rate or daily energy metabolism ((Lin et al., 2002; Oklejewicz & Daan, 2002; J R Speakman et al., 2003; Wiersma et al., 2004). However, other studies found no relationship between metabolism and longevity measured in voles ((Selman et al., 2008), blowflies *Calliphora stygia* ((Hulbert et al., 2004b), *Drosophila melanogaster* ((Hulbert et al., 2004a). Experiments where metabolism was manipulated by a cold exposure have failed to have impacts on both oxidative stress and longevity in short tailed field voles (*Microtus agrestis*) (Selman et al., 2008) and on longevity in mice (Vaanholt et al., 2008). Increased metabolism through exercise also had no effects on longevity in mice ((Vaanholt, et al., 2010). However, some other studies where energy expenditure has been manipulated have revealed a negative relationship between energy expenditure and life span (Daan, et al., 1996; Lemon & Barth, 1992), consistent with the predictions of the ROL theory. It has been demonstrated that most of the previous studies examining the link between metabolism and life span across species were performed using inappropriate statistical analysis, in which a correction for body size and phylogenetic independence effects were not applied (Furness & Speakman, 2008; Speakman, 2005).

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