



Age-related changes of physiological performance and survivorship of bank voles selected for high aerobic capacity



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ABSTRACT

Variation in lifespans is an intriguing phenomenon, but how metabolic rate influence this variation remains unclear. High aerobic capacity can result in health benefits, but also in increased oxidative damage and accelerated ageing. We tested these contradictory predictions using bank voles (*Myodes = Clethrionomys glareolus*) from lines selected for high swim-induced aerobic metabolism (A), which had about 50% higher maximum metabolic rate and a higher basal and routine metabolic rates, than those from unselected control lines (C). We measured sprint speed (VS_{max}), forced-running maximum metabolic rate (VO_{2run}), maximum long-distance running speed (VL_{max}), running speed at VO_{2run} (VVO₂), and respiratory quotient at VO_{2run} (RQ) at three age classes (I: 3–5, II: 12–14, III: 17–19 months), and analysed survivorship. We asked if ageing, understood as the age-related decline of the performance traits, differs between the A and C lines. At age class I, voles from A lines had 19% higher VO_{2run}, and 12% higher VL_{max}, but tended to have 19% lower VS_{max}, than those from C lines. RQ was nearly 1.0 for both A and C lines. The pattern of age-related changes differed between the lines mainly between age classes I and II, but not in older animals. VS_{max} increased by 27% in A lines and by 10% in C lines between age class I and II, but between classes II and III, it increased by 16% in both selection directions. VO_{2run} decreased by 7% between age class I and II in A lines only, but in C lines it remained constant across all age classes. VL_{max} decreased by 8% and VVO₂ by 12% between age classes II and III, but similarly in both selection directions. Mortality was higher in A than in C lines only between the age of 1 and 4 months. The only trait for which the changes in old animals differed between the lines was RQ. In A lines, RQ increased between age classes II and III, whereas in C lines such an increase occurred between age classes I and II. Thus, we did not find obvious effects of selection on the pattern of ageing. However, the physiological performance and mortality of bank voles remained surprisingly robust to ageing, at least until the age of 17–19 months, similar to the maximum lifespan under natural conditions. Therefore, it is possible that the selection could affect the pattern of ageing in even older individuals when symptoms of senility might be more profound.

1. Introduction

One of the most intriguing phenomena of evolutionary biology is the variation in lifespans and underlying mortality patterns across the tree of life. Even closely related, or individuals of the same species, can have very different average lifespans (Barja, 2013; Jones et al., 2014), which cannot be explained solely by differences in environmental factors. Therefore, the presence of such variation still requires to be explained in the context of evolutionary theory and also by the underlying physiological mechanisms. Ageing is a complex process, and detrimental changes occur simultaneously at various levels of biological

organization. Senescence is typically defined as an increase of mortality and decline in fertility with age after maturity (Schaible et al., 2015), but it is also manifested as decreased quality of life caused by a declined physiological performance (Margolick and Ferrucci, 2015). The pattern of this decline appears similar in various species and taxa, therefore, a decrease of physiological performance is commonly used in medical and evolutionary-ecology studies as a proxy of the ageing process (Marck et al., 2016).

An increased physiological aerobic performance, associated with regular physical activity, is well documented to be associated with a wide range of health benefits and prevents or even reduces symptoms of

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age-related disorders, such as obesity, diabetes, inflammation (Kokkinos and Myers, 2010) and cardiovascular diseases (Thompson, 2003). Therefore, increased physiological performance contributes to healthy ageing and prolonged lifespan. On the other hand, it has been shown that high aerobic capacity is correlated with increased basal and routine metabolic rates (Sadowska et al., 2015; Wone et al., 2015), which, according to the classical ‘rate of living’ (ROL) theory, is negatively correlated with lifespan (Rubner, 1908; Pearl, 1928).

One of the leading mechanistic explanations behind the hypothetical metabolism - rate of living nexus used to be the ‘free radical theory’ of ageing (FRT) (Harman, 1956). It was based on the assumption that high overall rates of aerobic metabolism can be associated with the excessive production of reactive oxygen species (ROS). Surplus ROS can damage mitochondria, which in turn produce more ROS. Therefore, this can lead to oxidative stress, manifested by increased oxidative damage to molecules, such as protein carbonylation or epigenetic changes to DNA, and hence accelerated ageing (Bratic and Trifunovic, 2010). However, although it is known that oxidative stress is associated with age-related diseases such as cancer, atherosclerosis, diabetes, heart and neurodegenerative diseases (Ortuño-Sahagún et al., 2014), the role of ROS as a factor underlining ageing remains unclear (Selman et al., 2012). This is not only because animals can increase the efficiency of anti-oxidative defence systems (Vaanholt et al., 2008), but also because ROS help to maintain homeostasis at a cellular level by playing important roles in intracellular signalling of various physiological processes (Zarse et al., 2012). Moreover, exercise-induced ROS can even prolong lifespan (Ristow and Schmeisser, 2014). The other plausible and widely discussed mechanistic explanations of ageing include shortening of telomeres, a limited number of cell divisions, disrupted protein turnover equilibrium, or accumulation of somatic mutations to nucleic and mitochondrial DNA with progressive age (Balcombe and Sinclair, 2001), i.e. processes that can also depend on the rate of metabolism. Thus, the actual mechanistic explanation behind the ROL theory remains a subject of debate.

Irrespective of the ambiguities concerning a hypothetical mechanism underlying the association between metabolic rate and ageing, extensive studies on a wide range of species cast serious doubts on the association itself. Comparative analyses showed no clear correlation between lifespan and the rate of metabolism (De Magalhães et al., 2007), or even a reversed pattern to that predicted by the ROL theory (Barja, 2004; Brunet-Rossini and Austad, 2004; Ricklefs, 2010; Montgomery et al., 2011; McNab, 2005). Analyses of several intra-specific correlations showed confusing results (Speakman et al., 2003, 2004; Oklejewicz and Daan, 2002; Niitepöld and Hanski, 2013; Hulbert et al., 2004; Melvin et al., 2007). Results of studies based on experimental manipulation of energy expenditure were also contradictory: average lifespan increased in response to elevated exercise in mice and rats (Chigurupati et al., 2008; Holloszy, 1997; Navarro et al., 2004), but mice selectively bred for high wheel-running activity had higher metabolic rate and shorter lifespan than non-selected control ones (Vaanholt et al., 2010). However, the selected mice without access to wheels had a similar rate of metabolism to controls, yet their lifespan also decreased, indicating no clear link between energy expenditure and lifespan.

Locomotor performance is a complex trait, limited by various anatomical, morphological and physiological features, as well as the current health state (Swallow et al., 2009). Although all types of locomotor performance are susceptible to age-related disorders, the relevance of particular limiting features to the process of ageing varies among locomotor performance types (Koch and Britton, 2001; Koch et al., 2011; Dlugosz et al., 2009; Bundle and Weyand, 2012). For example, aerobic capacity, associated with long-distance running, can be compromised by multiple dysfunctions to the cardiovascular system and decreased mitochondria efficiency, which alters energy supply and muscle strength (Speakman et al., 2003; Vaanholt et al., 2010; Navarro et al., 2004). Some disorders can also be associated with changes in body

mass, possibly due to the degeneration of internal organs (Lessard-Beaudoin et al., 2015). Moreover, age-related muscle-tendon stiffness tends to increase limb load and cause posture or coordination disorders, which lead to gait abnormalities in both long- and short-distance running (Horner et al., 2011). Therefore, to obtain a relevant evaluation of the ageing process, various parameters of organismal performance must be assessed.

Experimental approaches used in many previous ageing-related studies primarily involved intra-specific correlations or phenotypic manipulations of metabolic rate, and such data are unable to be used to draw conclusions about genetic correlations between traits. A promising tool is offered by an experimental evolution approach, which enables to investigate genetically-based relations under a controlled experimental regime (Swallow et al., 2009). However, only a few selection experiments have focused on physiological performance traits (Swallow et al., 1998; Koch and Britton, 2001; Hayes and Garland, 1995; Konarzewski et al., 1997). Moreover, these studies have been based on model species, for which the observed effects can be strongly affected by domestication: laboratory mice and rats underwent a long-term selection for increased parameters of reproduction, rapid growth (Ricklefs, 2010; Selman et al., 2012) and sedentary phenotype (Garland et al., 2011). In this study, we took advantage of a unique experimental-evolution model system, based on a non-laboratory species, the bank vole (*Myodes = Clethrionomys glareolus*; Sadowska et al., 2008). The voles from lines selected for increased swim-induced aerobic metabolism achieved about 50% higher maximum rate of oxygen consumption compared to those from unselected control lines (Sadowska et al., 2015; Konczal et al., 2015). Furthermore, the selected voles have increased basal metabolic rate (Sadowska et al., 2015), daily activity and food consumption (Koteja et al., 2009; Dheyongera et al., 2016), and different expression of some genes involved in metabolism in the liver (Konczal et al., 2015).

We asked whether the selection for high aerobic metabolism affected the pattern of ageing at the organismal level. We investigated survivorship, body mass, and five aspects of locomotor performance: the maximum speed achieved during sprint and long-distance running (with gradually increasing speed), the maximum run-induced aerobic metabolic rate (VO_{2run}), respiratory quotient and the speed achieved at VO_{2run} . We expected that the physiological performance traits are improved in the selected compared to the control lines and that they decline with age, and asked whether and how survivorship and the age-related changes of performance are altered by the selection. Our previous studies showed that the selection resulted in both an elevated metabolic rate and improved locomotor performance (Sadowska et al., 2015; Jaromin et al., 2016), but not in an elevation of oxidative stress markers (in breeding young-adult females; Ołdakowski et al., 2015). However, the increased aerobic metabolism could lead to a ROS production rate that exceeds the antioxidant and repair systems capacity at senile age, and consequently, to oxidative damage and faster ageing. On the other hand, increased physical activity can be associated with health benefits, such as an augmented capacity of the cardiovascular and antioxidant systems, not only at a young age but also, or even particularly, at senescence (Koch et al., 2011; Vaanholt et al., 2008). If this is true, voles from the selected lines should be characterized by increased survivorship and a less profound age-related decline of organismal performance. Thus, contradictory predictions concerning the effect of the selection on the ageing pattern can be legitimately proposed.

2. Materials and methods

2.1. The experimental model

The work was based on an experimental evolution model system, in which four replicate lines of bank voles (*Myodes = Clethrionomys glareolus* Schreber 1780) were selected for high aerobic metabolism

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