

“Pull and push back” concepts of longevity and life span extension

Khachik Muradian

Received: 29 July 2013 / Accepted: 27 September 2013 / Published online: 11 October 2013
© Springer Science+Business Media Dordrecht 2013

Abstract The negative relation between metabolism and life span is a fundamental gerontological discovery well documented in a variety of ontogenetic and phylogenetic models. But how the long-lived species and populations sustain lower metabolic rate and, in more general terms, what is the efficient way to decline the metabolism? The suggested ‘pull and push back’ hypothesis assumes that decreased P_{O_2} (hypoxia) and/or increased P_{CO_2} (hypercapnia) may create preconditions for the declined metabolic and aging rates. However, wider implementation of such ideas is compromised because of little advances in modification of the metabolic rate. Artificial atmosphere with controlled P_{O_2} and P_{CO_2} could be a promising approach because of the minimal external invasions and involvement of the backward and forward loops ensuring physiological self-regulation of the metabolic perturbations. General considerations and existing data indicate that manipulations of P_{CO_2} may be more efficient in life span extension than P_{O_2} . Thus, maximum life span of mammals positively correlates with the blood P_{CO_2} and HCO_3^- but not with P_{O_2} . Yet, proportional decrease of the body P_{O_2} and increase of P_{CO_2} seems the most optimal regime ensuring lower losses of the energy equivalents.

Furthermore, especially rewarding results could be expected when such changes are modeled without major external invasions using the animals’ inner capacity to consume O_2 and generate CO_2 , as it is typical for the extreme longevity.

Keywords Aging · Metabolism · Artificial atmosphere · Life span extension · Extreme longevity

Abbreviations

ETC	Electron transport chain
$FADH_2$	Reduced flavinadeninedinucleotide
LSE	Life span extension
MLS	Maximum life span
NAD^+	Oxidized nicotineamideadeninedinucleotide
$NADH$	Reduced nicotineamideadeninedinucleotide
P_{O_2}	Partial pressure of O_2
P_{CO_2}	Partial pressure of CO_2
ROS	Reactive oxygen species
V_{O_2}	Rate of O_2 consumption
V_{CO_2}	Rate of CO_2 production

Introduction

Life span extension (LSE) is an aim as desirable as difficult. Despite the recent advances in the field, the inverse relation between longevity and metabolism,

K. Muradian (✉)
State Institute of Gerontology of National Academy of
Medical Sciences of Ukraine, 67, Vyshgorodskaya Str.,
Kiev 04114, Ukraine
e-mail: kkm@geront.kiev.ua

first shown by Max Rubner over a century ago, remains the basic founding of LSE. There are reasonable recommendations to check whether the declined aging rate is associated with lower metabolism or food consumption in all cases of LSE claiming (Spindler 2012). Nevertheless, it was surprising to find out that the idea could be known from the ancient times, as it follows from the citation taken from the book of Aristotle. Around 350 years bc, Aristotle wrote: “...the natural warmth...consumes the material in which it is located...the lesser flame takes a long period to expend” (Aristotle, p. 4, eBooks@Adelaide) (Aristotle 2007). Unfortunately, attempts of LSE based on declined metabolism have often been compromised because of the difficulties in chronic modification of the metabolic rate. At least all our efforts to decrease the metabolic rate and extend life span due to application of the known inhibitors of mitochondrial or nuclear replication, transcription, translation and uncoupling resulted in only marginal effects, primarily because of the adverse side-effects of the life-long xenobiotics consumption (Frolkis and Muradian 1991). From this point of view, artificial atmosphere with controlled partial pressure of O_2 (P_{O_2}) and CO_2 (P_{CO_2}) seems more safe and promising approach because of the minimal external invasions and possible involvement of numerous forward and backward loops ensuring physiologically balanced self-regulation of the metabolic perturbations.

‘Pull and push back’ concept of longevity

There is an important conceptual and applied question: how the long-lived species and populations sustain lower metabolic rate and, in more general terms, what is the efficient way to decline the metabolism? To answer the question, we developed a working hypothesis named ‘pull and push back’. The essence of the hypothesis is schematically described using the ‘black box’ principle (Fig. 1).

The “black box” allows predicting the behavior of a system without any knowledge of its internal structure by monitoring the input and output signals. Application of the “black box” principle is especially appropriate to bypass the inconceivable complexity of the bioenergetics. As it follows from Fig. 1, the most relevant input signals could be O_2 and food consumption, whereas corresponding output signals are CO_2



Fig. 1 The “black box” scheme of the substrate and gaseous streams of the energy generation

and waste production. Definitely, there are two relatively independent streams: gaseous and substrate. At the other hand, the streams are closely intertwined, and hypoxic and hypercapnic atmospheres could have many common regulatory and metabolic channels with calorie restriction, except that the latter allows manipulating only the input substrate signals, whereas in artificial atmospheres both the input and output gaseous signals could be purposefully modulated. Thus, if the idea is to extend life span by slowing down the metabolic rate, it could apparently be done either by decreasing the partial pressure of O_2 (P_{O_2}), i.e. kind of “pulling” the stream back at the very beginning, or by increasing the partial pressure of CO_2 (P_{CO_2}) at the outlet and “pushing” the stream back, or both. In more formal terms, the ‘pull and push back’ hypothesis sounds as: decreased P_{O_2} (hypoxia) and/or increased P_{CO_2} (hypercapnia) may create preconditions for the declined metabolic and aging rates.

According to the hypothesis, there should be a negative correlation between the P_{O_2} and maximum life span (MLS), whereas the corresponding correlation with P_{CO_2} should be positive. A priori, the first correlation seems more reasonable because long-lived species usually have lower O_2 consumption rate (V_{O_2}). We checked validity of the predictions on mammals with different MLS, taking the longevity records from the AnAge database (Tacutu et al. 2013) and P_{O_2} or P_{CO_2} data from papers available in the PubMed. Surprisingly, we failed to find the expected negative correlation between the P_{O_2} and MLS ($P > 0.2$), whereas the less expected positive correlation between P_{CO_2} and MLS was statistically significant ($P < 0.02$) (Fig. 2).

But how the species with lower V_{CO_2} sustain higher P_{CO_2} ? The simplest answer could be associated with the lower ventilation rate and gradual accumulation of CO_2 . However, this suggestion was not confirmed, at least, when analyzing correlation between MLS and the alveolar – arterial difference ($A-a$) (Fig. 3).

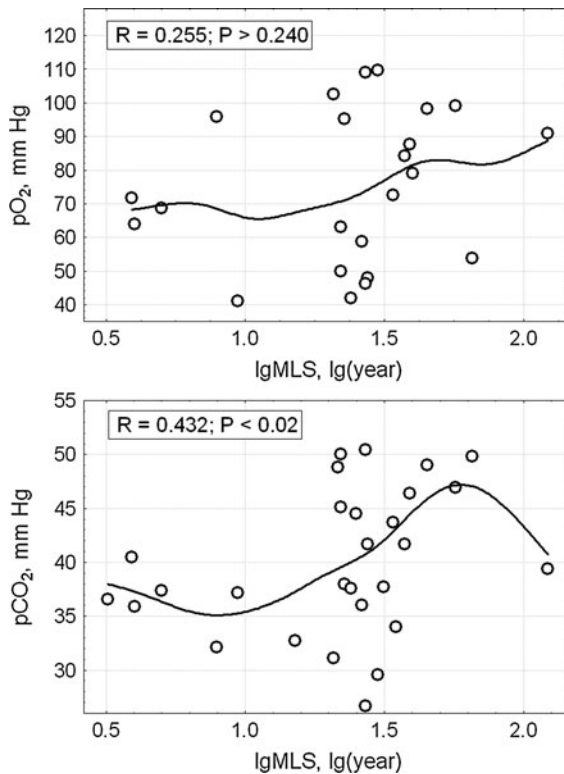


Fig. 2 Correlation of MLS with P_{O_2} and P_{CO_2} in the blood of mammals

Because lower A–a means a better ventilation, the observed negative correlation between A–a and MLS suggests that long-lived species could actually have higher ventilating capacity. Another possible cause of the higher P_{CO_2} could be related to higher HCO_3^- concentrations, in view of a well-known positive relation between the CO_2 and HCO_3^- . A significant positive correlation between the blood HCO_3^- and MLS has been found ($P < 0.01$). The higher HCO_3^- in the blood of long-lived species may indicate superior buffering and maintenance of the acid–base balance, raising a possibility whether simple inorganic indices like CO_2 , HCO_3^- and H^+ could be determinants of longevity. In fact, cellular and organism levels of CO_2 , HCO_3^- and H^+ are tightly linked. Due to the carbonic anhydrases, CO_2 is in rapid equilibrium with H_2CO_3 , which in turn quickly dissociates into H^+ and HCO_3^- . Thus, changes to any member of this trio would provoke adequate shifts in the other two. In multicellular organisms, the homeostasis of CO_2 , HCO_3^- and H^+ is additionally ensured by coordinated functioning of specialized sensing cells which

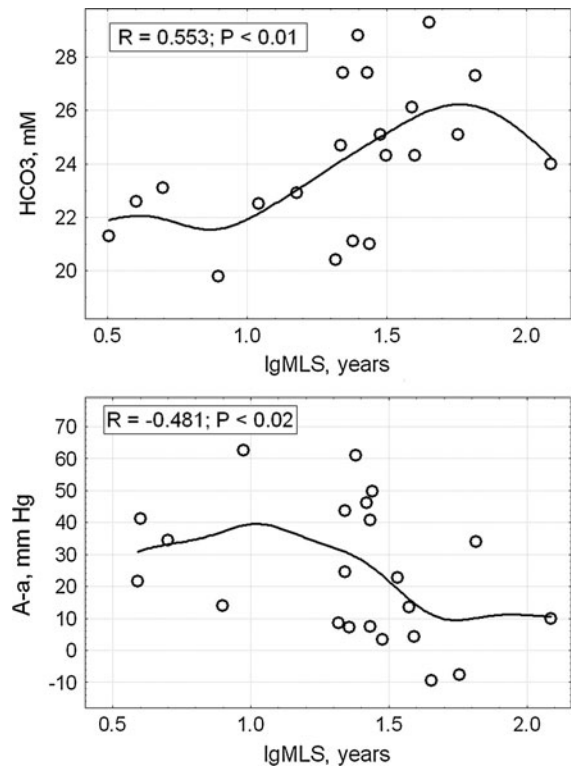


Fig. 3 Correlation of MLS with alveolar – arterial difference (A–a) and HCO_3^- in the blood of mammals

measure CO_2 , HCO_3^- and H^+ in their immediate environment and may trigger alterations in expression of downstream genes followed by physiological adjustments in the lung ventilation and metabolism (Tresguerres et al. 2010; Buck and Levin 2011; Lindinger and Heigenhauser 2012).

Differential role of O_2 and CO_2 in regulation of the metabolic rate and life span

O_2 and CO_2 are utilized and produced almost in equimolar amounts and are often regarded as a closely related pair of variables in the energy metabolism and determination of longevity (Frolkis and Muradian 1991; Lehmann et al. 2008; Furness and Speakman 2008). Nevertheless, their physiological role and targets are different and separated in time and space. In fact, most amount of CO_2 is generated during the three decarboxylations of pyruvate in the citric acid cycle (Meléndez-Hevia et al. 1996; Maina 2002). Energy released during the decarboxylation is used to

reduce NAD^+ to NADH and FAD^+ to FADH_2 , the carriers of the electrons from the mitoplasm to the electron transport chain (ETC). Of note, oxygen necessary for the generation of CO_2 is taken not from the O_2 molecules which are freely diffused in the mitoplasm but from the H_2O . P_{CO_2} can modify the energy generation rate primarily due to modulation of the decarboxylation. According to the Le Chatelier's principle, higher P_{CO_2} will stimulate the backward reaction thus decreasing the decarboxylation rate and vice versa ($\text{R-COOH} \leftrightarrow \text{RH} + \text{CO}_2$). In contrast, O_2 participates in the energy generation events occurring in the very "bottom" of the ETC, in the IV cytochrome-*c*-complex (Tan et al. 2004). Because O_2 does not directly participate in the citric acid cycle, it is tempting to speculate that in case of hypoxia the electrons duly transported by NADH and FADH_2 will accumulate in the ETC as a result of the O_2 deficit. This could provoke a dangerous overcrowding of the highly energized equivalents. In fact, NADH and FADH_2 could be regarded as 'supermacroergs' because their free energy is several times higher than that of ATP and other three-phosphates. It is understood that such highly charged agents can easily react and modify other 'innocent' by-standing molecules, especially the redox-sensitive compounds. Therefore, the hypoxia-induced electron 'traffic jam' will obviously be associated with ill-controlled side-effects, with involvement of NADH and FADH_2 , as well as elevated electron leakage and ROS generation in the ETC. On the other hand, hypercapnia could decline the rate of decarboxylation and result in a deficit of NADH and FADH_2 . However, the elevated demand would only stimulate unimpeded transportation of NADH and FADH_2 to the inner membrane and electrons current in the ETC. In general, a moderate deficit in the NADH and FADH_2 supply seems an optimal mode of energy metabolism because it assumes prompt utilization of NADH and FADH_2 and minimal side-effects. The participation of O_2 in the energy generation only at the very end of the ETC will obviously limit its regulatory repertoire. It could apparently be the result of relatively late appearance of O_2 in the atmosphere, because most part of evolution occurred in sever hypercapnia and at practically complete absence of O_2 in the atmosphere (Walker 1985; Goldblatt et al. 2006). Modern aerobic species, humans included, are extremely sensitive to the O_2

deficiency and could die within few minutes in the absence of O_2 supply, making hypoxia a favorite biological and clinical target. Nevertheless, O_2 may have restricted capabilities to modulate the energy generation. From this point of view, the influence of CO_2 on the metabolic regulation seems superior. Moreover, CO_2 has several unexpected protective capacities. For instance, it can directly interact with peroxynitrite and form nitrosoperoxycarbonate which is further hydrolyzed producing carbonate and nitrate, thus scavenging of peroxynitrite and preventing oxidative or hypoxic-ischemic damages (Vesela and Wilhelm 2002; Vannucci et al. 1995). Overall, the role of hypercapnia in regulation of the energy homeostasis and LSE seems underestimated. Yet, the proportional and simultaneous decrease of the body P_{O_2} and increase in P_{CO_2} seems the most optimal energy generation regime. Furthermore, better perspectives of LSE could be expected when such changes are modeled without major external invasions, i.e., using the animals' inner capacity to consume O_2 and generate equivalent amount of CO_2 , as it is typical for the extreme longevity. For instance, the most outstanding representative of such elite species, bivalve mollusk *Arctica islandica* could live over 500 years! It feeds and breathes during several hours in the sea water, digging afterwards into the bottom sand or mud for several days during which it is completely isolated from the external milieu and gradually accumulates the body CO_2 and depletes the stored O_2 (Strahl et al. 2011; Munro and Blier 2012). The phenomenon is typical for the other representatives of the extreme longevity.

Concluding remarks

The idea of negative relationship between the longevity and metabolism, apparently understood from the ancient times, is currently well documented in a variety of ontogenetic and phylogenetic models. Failures to extend life span by modulating the metabolic rate is mostly associated with the difficulty of long-term inhibition of the oxidative processes aggravated by the adverse side-effects of the lifelong application of the metabolic inhibitors. Artificial atmospheres seem more promising approach for the safe metabolic modulations because of the minimal

external invasions and involvement of the backward and forward loops ensuring physiological self-regulation. The proposed “pull and push back” concept assumes that decreased P_{O_2} and/or increased P_{CO_2} can contribute to the decline in metabolic and aging rates. The idea has been supported by the positive correlation of mammalian MLS with the blood P_{CO_2} or HCO_3^- , as well as by our direct experiments with lifetime hypoxia and hypercapnia (Muradian 2008). Nevertheless, proportional and simultaneous decrease of the body P_{O_2} and increase of P_{CO_2} seems the most optimal energy generation regime, apparently utilized by the species with extreme longevity.

Acknowledgments The author is grateful to Prof. Vadim Fraifeld for the support and guidance from the very beginning of the concept development and for the invaluable editorial contribution in preparation of the manuscript.

References

- Aristotle On longevity and shortness of life (2007). The University of Adelaide Library, eBooks@Adelaide
- Buck J, Levin LR (2011) Physiological sensing of carbon dioxide/bicarbonate/pH via cyclic nucleotide signaling. *Sensors* 11:2112–2128
- Frolkis VV, Muradian KK (1991) Life span prolongation. CRC Press, Boca Raton
- Furness LJ, Speakman JR (2008) Energetics and longevity in birds. *Age (Dordr)* 30:75–87
- Goldblatt C, Lenton TM, Watson AJ (2006) Biostability of atmospheric oxygen and the great oxidation. *Nature* 443:643–645
- Lehmann G, Segal E, Muradian KK, Fraifeld VE (2008) Do mitochondrial DNA and metabolic rate complement each other in determination of the mammalian maximum longevity? *Rejuvenation Res* 11:409–417
- Lindinger MI, Heigenhauser GJ (2012) Effects of gas exchange on acid–base balance. *Compr Physiol* 3:2203–2254
- Maina JN (2002) Fundamental structural aspects and features in the bioengineering of the gas exchangers: comparative perspectives. *Adv Anat Embryol Cell Biol* 163:1–108
- Meléndez-Hevia E, Waddell TG, Cascante M (1996) The puzzle of the Krebs citric acid cycle: assembling the pieces of chemically feasible reactions, and opportunism in the design of metabolic pathways during evolution. *J Mol Evol* 43:293–303
- Munro D, Blier PU (2012) The extreme longevity of *Arctica islandica* is associated with increased peroxidation resistance in mitochondrial membranes. *Aging Cell* 11:845–855
- Muradian KK (2008) Atmosphere, evolution, rejuvenation and life span extension. *Probl Aging Longev* 17:457–477 (in Russian)
- Spindler SR (2012) Review of the literature and suggestions for the design of rodent survival studies for the identification of compounds that increase health and life span. *Age (Dordr)* 34:111–120
- Strahl J, Brey T, Philipp EE, Thorarinsdóttir G, Fischer N, Wessels W, Abele D (2011) Physiological responses to self-induced burrowing and metabolic rate depression in the ocean quahog *Arctica islandica*. *J Exp Biol* 214:4223–4233
- Tacutu R, Craig T, Budovsky A, Wuttke D, Lehmann G, Taranukha D, Costa J, Fraifeld VE, de Magalhães JP (2013) Human ageing genomic resources: integrated databases and tools for the biology and genetics of ageing. *Nucleic Acids Res* 41(Database issue):D1027–D1033
- Tan ML, Balabin I, Onuchic JN (2004) Dynamics of electron transfer pathways in cytochrome C oxidase. *Biophys J* 86:1813–1819
- Tresguerres M, Buck J, Levin LR (2010) Physiological carbon dioxide, bicarbonate, and pH sensing. *Pflugers Arch* 460:953–964
- Vannucci RC, Towfighi J, Heitjan DF, Brucklacher RM (1995) Carbon dioxide protects the perinatal brain from hypoxic to ischemic damage: an experimental study in the immature rat. *Pediatrics* 95:868–874
- Vesela A, Wilhelm J (2002) The role of carbon dioxide in free radical reactions of the organism. *Physiol Res* 51:335–339
- Walker JC (1985) Carbon dioxide on the early earth. *Orig Life Evol Biosph* 16:117–127