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MINI-REVIEW

Neotenic Traits in *Heterocephalus glaber* and *Homo sapiens*

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Abstract—The data on the neoteny (prolongation of youth and retardation of aging) in naked mole rat (*Heterocephalus glaber*) and *Homo sapiens* are summarized. Fifty-eight neotenic traits have been described by now in the naked mole rat at the organismal, tissue, cellular, and metabolism levels. Among them, there are traits that increase the lifespan, including mild depolarization of mitochondria that prevents generation by these organelles of reactive oxygen species known to strongly promote aging. Mild mitochondrial depolarization disappears with age in short-lived mammals (mouse *Mus musculus*) much faster than in long-lived mammals (e.g., naked mole rats and bats). The development of neoteny in naked mole rats has been due to the social organization. These animals live in subterranean colonies, where sexual reproduction is monopolized by the queen and one or several males who are defended and provided with nutrition by numerous subordinates. Humans have achieved a gradual increase in the lifespan first due to neoteny, and then to the technical progress, which can be observed by comparing the lifespan curves of chimpanzees, hunter-gatherers of the Paraguayan Ache tribe, and residents of Sweden from the XVII century to the present day. Significantly different rates of neoteny and technical progress make it possible to discriminate between the contributions of these two longevity mechanisms.

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In 2015, our group in Moscow together with the group of T. Hildebrandt in Berlin [1-3] and an independent joint group of T. Park in Chicago, Stockholm, and Vienna [4] have focused on studying the traits of neoteny (i.e., prolongation of lifespan due to slowing down ontogenetic programs) in the naked mole rat *Heterocephalus glaber*. The lifespan of this rodent is at least tenfold longer than the lifespan of mice or rats [5]. Many such traits have been described in the article published in *Physiological Reviews* by the Moscow and Berlin groups [3]. In total, 43 manifestations of ontogenesis were mentioned that were absent in naked male rats or appeared in their development essentially later than in mice and other members of the Bathyergidae family from which the naked mole rat had diverged more than 30 million years ago.

Recognition of neoteny as a cause of longevity is often hindered by the trait mosaicism in the ontogenesis of a neotenic organism. This is because the evolution of a species can be determined not only by the deceleration of ontogenesis, but also by some other factors that require ontogenesis acceleration rather than deceleration. Thus, mosaicism [6] prevented the acceptance of the hypothesis by L. Bolk about the neoteny of *H. sapiens* [7, 8].

Factors important for elucidation of such circumstances include the extent of diversity of neotenic traits and their possible role in the control of the lifespan of species members. Here, we present an addition to the list of neotenic traits of naked mole rats described within the last two years after our publication in *Physiological Reviews* in 2017 [3] (see also [5]). This list has now grown from 43 to 58 traits, and, which is especially important, was supplemented with the traits that determine the lifespan.

In 2018-2019, M. Yu. Vyssokikh and colleagues from the Moscow group detected mild depolarization of mitochondria inherent almost in all mammalian tissues. This regulatory mechanism plays the major role in the prevention of reactive oxygen species (ROS) generation by the mitochondria. Mild depolarization of mitochondria disappears by the end of life in common mammals, such as the mouse *Mus musculus*; however, it is retained for decades in long-lived animals, such as naked mole rats and bats [9]. Our results confirmed the hypothesis on the role of mitochondrial ROS as toxins produced by the organism itself and gradually suppressing its functions, being the cause of senescence [10].

It is interesting to compare the role of neoteny in the longevity of naked mole rats and humans, who are also

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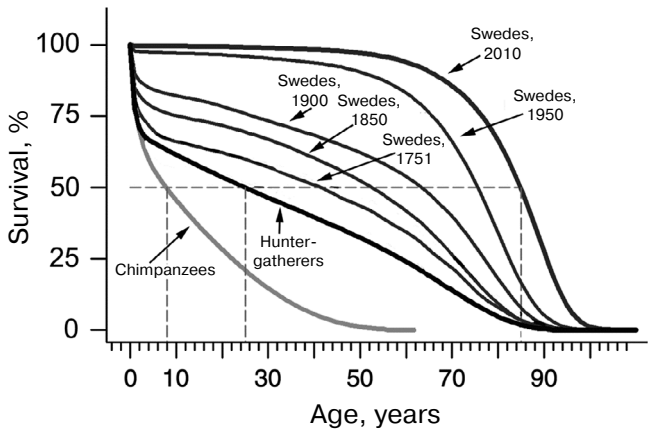
social beings. According to the data of Burger et al. [11, 12], the survival of humans in modern civilization is close to 100% up to the age of ~60 years, after which the survival rate increasingly falls and reaches 50% annual mortality in Swedes by the age of 90 (figure). The natives of the Paraguayan Ache tribe have 50% survival at the age of 28, while chimpanzees have 50% survival at the age of 9. The 3-fold decrease in the mortality of Paraguayan Ache natives as compared to chimpanzees appears to be due to the collective activities, such as defending the tribe, using the simplest work tools, building shelters, as well as higher intellectual development compared to chimpanzees. Further decrease in the mortality is caused by the technological progress, the development of which is incomparably faster than the rate of the biological evolution.

The table shows neoteny traits in naked mole rat and humans.



Age-related dependence of survival in Swedes (in 1751, 1850, 1900, 1950, and 2010), chimpanzees, and hunter-gatherers of the Paraguayan Ache tribe [11, 12]

Neotenic features of naked mole rat and human at the different level of organization

Level of organization	Naked mole rat	Human	Common traits of human and naked mole rat
1	2	3	4
Organism	considerably smaller body mass than in 20 related species of the Bathyergidae family [3, 13]; absence of hair (unique among adult rodents) [3, 14, 25]; much more prolonged gestation than expected for animals with comparable body mass [13, 15-17]; much longer growth and maturation time, than for other rodents [3, 16]; increase in reproductivity with age (vs. decrease observed in other mammals) [3, 18]; limited ability to maintain constant body temperature (similar to newborn animals) [3, 19-21]; age-related diseases, such as cancer, diabetes, cardiovascular disorders, liver and brain pathologies, kidneys diseases, and many infections, are very rare or absent as the causes of death of naked mole rats (as is the case in mammalian juveniles) [3, 22, 23]; delayed maturation of the skeleton system [3, 24]; high maximal lifespan; low mortality level (as compared to other rodents) that increases only insignificantly, at least during the first 24 years of life [3, 19, 23]; absence of age-related decrease in cognitive functions [3, 23]	“flat face”, orthognathy [8]; reduction or absence of body hair [8]; central position of the foramen magnum (it migrates backward during the ontogeny of most other primates) [8]; retention of cranial structures until the advanced age [8]; structure of hands and legs [8]; form of the pelvis [8]; ventrally directed position of the sexual canal in women [8]; certain variations of tooth rows and cranial sutures [8]; absence of cranial crests [8]; absence of brow ridges [8]; thinness of skull bones [8]; position of the orbits under the cranial cavity [8]; brachycephaly [8]; small teeth [8]; late eruption of teeth [8]; impossibility of full rotation of the thumb [8]; prolonged period of infantile dependency [8]; prolonged period of growth [8]; long lifespan [8]; short extremities compared to body size [8]; legs are longer than arms [3]; vertical position of the body [3]; longer gestation time in comparison to chimpanzees [3]	absence or reduction of hair; long lifespan and healthspan; long period of growth; long period of gestation; long period of helpless infancy; long period of sexual maturation

Table (Contd.)

1	2	3	4
Tissue	absence of auricles, as in newborns and in contrast to other adult mammals [3, 26]; absence of scrotum, as in newborns [3, 16, 27]; neonatal-type distribution of calbindin in the CA3 region of the hippocampus [3, 28]; low sensitivity of hippocampus to exogenous adenosine [3, 28, 29]; very long time-frame for brain development compared to that of other rodents [4]; underdevelopment of numerous morphological aspects of the lungs [3, 30, 31]; newborn naked mole rat brains are twice as large as newborn mouse brains which are ~17% of adult mass at birth but by 2 weeks attain 90% of adult mass, whereas naked mole rat brains are ~41% of adult size at birth, but do not reach 90% of adult mass until 3 month of age. Through the age of weaning naked mole rat brains are significantly larger than mice, however adult naked mole rat brains are significantly smaller than mice especially when accounting for body mass [5]; naked mole rats are born with a well-defined dentate gyrus (DG) molecular layer with significantly fewer cells expressing Sox2, whereas nearly all dentate gyrus cells in newborn mouse brains are Sox2 positive. Both species are born with comparable levels of Sox2 expressing cells in ventricular and subventricular zones (VZ and SVZ respectively), but this level dramatically drops in mice during first postnatal week, however in naked mole rats level do not significantly changes between birth and 3 years of age [5]; very high resistance of brain neurons to anoxia and subsequent oxidative stress during reoxygenation (similar to newborn animals) [3, 29, 32]; lack of synaptic paired-pulse facilitation in contrast to the effects in other adult mammals [3, 28, 32]; retention of ability for regeneration and elongation of neurons in adult age [3, 23, 28, 33]; pulmonary neuroepithelial bodies, which normally decrease in number during the first postnatal week, are presented in high numbers in naked mole rats at ages greater than two weeks [3, 34]; absence of the decrease in the elasticity of blood vessels with age [3, 18, 25]; absence of the decrease in the brain cortex area with age [3, 18]; absence of age-related decrease in the mineral density of bones [3, 18, 25]; absence of any decline in the state of articular cartilage with age [3, 18]; sensitivity of naked mole rat smooth muscle to NO does not decrease with age, in contrast to changes observed in other rodents [3, 35, 36]; in mice cortical layer 1 does not become clearly defined until 2 weeks of age and loses DCX expression by 3 weeks. In contrast, naked mole rats are born with a more organized cortical arrangement and more developed cortical development at birth, nevertheless their period of cortical maturation is longer than that in mice [5]; firing pattern's level in mice reaches up its maximum value by 6 months since birth, whereas in naked mole rats this level slowly increases during the first life's decade [3, 4]	shape of the auricle [8]; epicanthal fold [8]; relatively large brain mass [8]; genital labia in women [8]; absence of baculum (penal bone) [3]; small nose [3]; humans retain more primitive shape of the skeleton and muscles, whereas in monkeys, the anatomy of these organs is more complicated and specialized [3]; human brain is much larger than the chimpanzee brain [3]; the growth rate of human brain increases until birth, whereas in chimpanzee, this parameter starts to decrease much earlier [3]; in adult humans, neurons retain definite “minor” characteristics, such as increased synaptic activity and plasticity, as well as incomplete myelinization during the first two decades of life [48]; spindle-shaped neurons are larger and more numerous in humans than in great apes [48]	very undeveloped vomeronasal organ (similar to neonates) [3, 23, 49]; increased synaptic activity and plasticity; incomplete myelinization of neutral fibers during several years after birth; the explosive formation of synapses (“surplus synaptogenesis”) at the early stages of brain development

Table (Contd.)

1	2	3	4
Cellular and molecular	absence of Ca^{2+} overload at the long-term excitation of neurons [3, 32, 37]; strong delay of the development of a united mitochondrial system during the postnatal period in skeletal muscles [2, 3]; increase (instead of decrease) in the number of mitochondria and their activity with age [2, 3, 23]; naked male rats, in contrast to mice, do not exhibit the age-related decrease in the respiratory control of mitochondria [9]; absence of age-related general decrease in metabolism [3, 18, 25]; absence of age-related increase in the lipid peroxidation index and lipid oxidative damage observed in other mammals with aging [3, 24, 35, 38]; ROS generation in naked mole rats does not increase with age (unlike in other mammals) [3, 9, 23]; naked mole rat axonal composition is more similar to humans, whereby naked mole rats maintain expression of 3R tau even after brain growth is complete, mice experience an abrupt downregulation of 3R tau by postnatal day 8 [5]; mild depolarization of mitochondria is retained in naked mole rats until the age of 10 years, whereas in mice, this mechanism of mitochondrial anti-ROS defense stops functioning already within a year after birth [9]; mild depolarization of liver mitochondria in naked mole rats is retained at least until 10 years of age, whereas in mice, it decreases immediately after birth [9]; inactivation of gene encoding FAS-activated serine/threonine kinase (FASTK), an antiapoptotic and proinflammatory enzyme [3, 33]; absence of age-related decrease in the levels of superoxide dismutases 1 and 2 and catalase [3, 9, 40, 41]; decrease in the level of adenine nucleotides in mitochondria of adult naked rats and higher level of respiration after exhaustion of added ADP (similar to rat and mouse embryos and newborns) [3, 32]; unusually high proteasomal activity in adult animals [3, 14, 23, 42, 43]; changes in the sequence of insulin B-chain leading to the decrease in the hormone activity to the embryonic level [3, 33, 44]; absence of decrease in the IGF2 level in adult naked mole rats [3, 33]; decrease in the expression of IGF-1, insulin-induced gene 2 (*INSIG2*) and increase in the expression of *IGF1R* and resistin (*RETN*) genes in adult naked mole rats [3, 33]; no perception of pain caused by capsaicin or acid due to the lack of substance P [3, 21]; presence of the glutamate NMDA receptor GluN2D subunit in adults, whereas other mammals have it only in neonates [9, 45]; absence of decrease in glucose tolerance in old animals [3, 18, 20]; absence of age-related increase in the level of glycated hemoglobin [3, 18, 46]; presence of high-molecular-weight hyaluronan in the intercellular space [3, 47]; in naked mole rats, the level of light chain neurofilaments (NF-L) increases by 33% by weeks 2-4 after birth; by 4 months, it is 168% higher than in the newborns. In mice, the level of NF-L increases rapidly after birth and reaches its adult level during the first postnatal week [5]; expression of DCX (microtubule-associated protein, doublecortin) in mice is higher than in naked mole rats, but rapidly decreases in both *gyrus dentatus* and subventricular zone, whereas in naked mole rats, its expression decreases gradually [5]; the level of Map2D isoform (microtubule-associated protein) remains stable in naked mole rats until 6 months of age, whereas in rats, expression of this protein falls completely by the postnatal weak 3 [5]; the synaptophysin level dramatically increases in naked mole rats at the age 2-4 months to 9 months, whereas in mice, this occurs on days 10-35 after birth [5]; expression of tyrosine hydroxylase in the brain of naked mole rats increases progressively from birth until 3 years of age, whereas in rats, this occurs faster – during weeks 4-5 of the development [5]; unlike mice, naked mole rats express myelin-associated glycoprotein (MAG) at birth [5]; in mice, hexokinase II dominates over more active hexokinase I in the muscle mitochondria until 3 months of age; in naked mole rats – until 10 years [9]		both species have the highest numbers of the PXXP motifs in proline-rich domain of p53 (5 for humans and 4 for naked mole rats); the level of tyrosine hydroxylases increases until the age of 2-3 years; steady expression of 3R tau protein

Conflict of interest. The authors declare no conflict of interest.

Compliance with ethical standards. This review does not describe experiments performed with animals or humans by any of the authors.

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