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Regular Article

Naked mole rat workers and dispersers are susceptible to hyperoxia when exercising in captivity

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Abstract Naked mole rats have putative 'subcasts' that perform various functions within the colony. Workers and dispersers are the most active mammals, as they perform the bulk of the colony's labor, while others remain in the nest. Naked mole rats are kept in conditions far removed from their natural habitat, as they live in underground burrows containing approximately 8–15% oxygen and perform heavy physical labor to maintain their colony. Hyperoxia is one of the factors that increase reactive oxygen species in the body. Physical exercise under these conditions can lead to oxidative damage to organs due to exposure to high oxygen levels. To study this, we placed a chamber containing clay with a density similar to that found in the Horn of Africa in a captive naked mole rat colony. To identify active naked mole rats, we conducted accelerometry and thermometry in a separate colony and found that animals with low temperatures were workers and dispersers who had abandoned their nests. After placing a clay chamber, abnormal animals with sunken sides emerged. MicroRNA expression analysis revealed oxidative damage to the heart, skeletal muscles, and kidneys. Therefore, increasing colony exercise under hyperoxic conditions will lead to the death of workers and dispersers.

1 Introduction

Like other members of the family Bathyergidae, naked mole rats (*Heterocephalus glaber*) are subterranean rodents and are unique to the Horn of Africa (Somalia, Ethiopia). They possess distinctive features such as the absence of skin hair, which distinguishes them from all African mole rats, eusociality, and an abnormally long lifespan among all Bathyergidae [1–3]. Naked mole rats, which weigh relatively little (30–80 g), can live up to 37 years in laboratory conditions [4], while a rodent of the same weight (e.g., the house mouse *Mus musculus*) can live up to 3 years in laboratory conditions and up to 1.5 years in the wild [5]. Due to their extraordinary biological characteristics, naked mole rats are among the most interesting mammals for research, especially in the field of longevity research, but another interesting topic is their eusociality.

The information obtained from experiments with naked mole rats has some limitations because naked mole rats are kept in conditions that do not reflect their natural habitat. First, these animals are oddly adapted to hypoxia (8–15% O_2 in ambient air underground) due to their underdeveloped lungs [6, 7], but the ambient air in captivity contains 21% O_2. Although there have been studies reporting 21% O_2 in the air of naked mole rat burrows [8], we consider this oxygen content to be hyperoxic due to the extreme tolerance of these animals to hypoxia, even anoxia [9], and high levels of lipid peroxidation in tissues, even at a young age [10]. Second, naked mole rats in captivity do not experience sufficient exercise as in the natural habitat, since they do not dig burrows, forage for food, or fight predators. Therefore, we decided to study the effects of high physical activity in a hyperoxic environment

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on naked mole rats, pursuing two goals. The first was to enrich the naked mole rat's habitat. The second was to study the potential negative effects of hyperoxia during physical activity.

To achieve our goals, we monitored body mass index for 3 years and then studied microRNA in organs that may be susceptible to hyperoxia: the heart, kidneys, liver, and skeletal muscles.

The study of microRNAs was motivated by the fact that the naked mole rat transcriptome is currently understudied. MicroRNAs are highly evolutionarily conserved across species and effectively regulate the expression of numerous genes [11].

2 Methods

2.1 Animal care and maintenance

Two colonies of naked mole rats, 13 and 11 individuals were obtained from the Leibniz Institute for Zoos and Wildlife (IZW) (Berlin, Germany). These colonies were subsequently expanded at the A.N. Belozersky Research Institute of Physicochemical Biology, Moscow State University, to 54 and 32 individuals before the start of the study. Each animal was individually identified within the colony using a subcutaneous RFID chip. Naked mole rats were maintained in cylindrical plastic containers connected by plastic tubes at a temperature of 27 ± 1 °C and a humidity of 50 ± 10% with a 12:12-h light/dark cycle (10:00–22:00). The animals were fed apples, sweet potatoes, carrots, and cereals daily. Naked mole rats do not require drinking water, as their physiology allows them to obtain water only from solid food. To enrich the habitat of naked mole rats, a rectangular container filled with dense clay, simulating the soil typical of the animals' natural habitat, was placed in the colony. The container was immediately removed after signs of cachexia appeared in 9 of 54 individuals (3 females and 6 males aged 2–6 years). To monitor the condition of these animals, the body mass index of age-matched control animals (n = 9, 4 females and 5 males) was measured every 4–5 months. Animals were euthanized by decapitation after anesthesia with an inhalation solution of isoflurane (Laboratorios Karizoo. S.A., Spain) 5% at a flow rate of 0.4 L/min using an R500 apparatus (RWD, China).

2.2 Experimental groups of animals

Two groups of naked mole rats were selected for the microRNA study. The first group consisted of healthy animals (n = 3, 1 female and 2 males) with a body (abdominal surface) temperature of 30 °C and a body mass index of 0.33. The second group consisted of animals with idiopathic cachexia and asthenic body constitution (n = 3, 2 females and 1 male) with a body temperature of 27 °C and a body mass index of 0.25.

2.3 Body mass index calculation

The body mass index (BMI, g/cm^2) was calculated using the following formula: BMI = animal weight, g/(animal length, cm)^2.

2.4 Body surface temperature measurement

The abdominal surface area of the animals was measured using a medical infrared thermomether B.Well WF-4000 in surface measurement mode (B.Well, Switzerland).

2.5 Isolation and sequencing of microRNA

Liver, kidney, heart, and skeletal muscle samples were collected from each animal. RNA fractions containing microRNAs were isolated from the tissue samples using commercial miRNEasy kits (Qiagen, USA). The resulting samples were used to generate cDNA libraries for subsequent sequencing. The quality of the isolated fractions was assessed using microelectrophoresis on Bioanalyzer chips (Agilent, USA). Samples with an RNA integrity index (RIN) of at least 8 were selected for sequencing.

Sequencing was performed on the NextSeq platform (Illumina, USA) using the NextSeq 500/550 High Output v2 kit (Illumina, USA). cDNA libraries from isolated RNA samples were prepared using NEBnext kits (NEB, USA) according to the instructions. Qualitative and quantitative library analysis was performed using Bioanalyzer microelectrophoresis (Agilent, USA) and Qubit fluorimetry (ThermoFisher, USA). Sequencing quality was assessed using the BaseSpace service (Illumina, USA) using the following parameters: cluster density, signal intensity in the detection channels, and the proportion of clusters passing the filter, based on the yield of aligned reads. All parameters were within acceptable limits.

2.6 Bioinformatics analysis of microRNA sequencing data

The nucleotide sequences (reads) obtained from sequencing underwent mandatory quality assessment using the fastqc program; high-quality reads (> 30) were filtered out for further analysis. Adapters were removed using the cutadapt program. After this, only sequences of 18–31 nucleotides in length were selected for further analysis. A microRNA search was performed using the mirDeep2 algorithm based on the naked mole rat genome, using information from a related genome (*Mus musculus*). Random and/or non-specific sequences were then removed from the overall list of sequences. Only sequences present in more than 60% of samples from their subgroup (experimental or control group of the corresponding tissue or organ) and that passed all quality filters were selected for further analysis.

2.7 Annotation and analysis of microRNAs

For sequences that passed all filters, differential miRNA expression between healthy animals and animals with spontaneous idiopathic cachexia was calculated using DESeq2. Human orthologs were searched for using blastn, using the Mirbase v.22 human miRNA database (https://mirbase.org) as a comparison database. Potential miRNA targets were searched using the miRDB miRNA-target interaction database (https://mirdb.org/mirdb). Only miRNA targets with a target score > 80 were selected from the miRDB database. The miRNA-target interactions identified by this method were manually analyzed using the UniProt, NIH Gene, and scientific article databases.

2.8 Statistical analysis

The data were processed in RStudio 2024.04.02 Build 764 (Posit, USA) with the dplyr, ggplot2, ggsignif, patchwork, and readxl packages. The Shapiro–Wilk and Kolmogorov–Smirnov tests were used to test for normality of distribution if the number of data points exceeded 5000. For multiple comparisons of independent groups, the Kruskal–Wallis and Conover-Iman tests were used. The Levene test was used to test for homogeneity of variance. Data from dependent groups were examined using the Friedman and Wilcoxon tests. Comparisons of two groups were examined using the Mann–Whitney U test. Differences were considered statistically significant at $p < 0.05$; for multiple comparisons, the p level was adjusted using the Benjamini and Hochberg corrections.

3 Results

3.1 Animal phenotype

Naked mole rats began digging holes in the ground almost immediately. We assumed this was a normal reaction. However, after 6 months, we noticed the first external changes in some naked mole rats. They began losing weight; their facial features became more pointed, reminiscent of those in animals suffering from cachexia; their body surface temperature was lower than normal. We hypothesized that this was caused by depletion of subcutaneous fat and muscle atrophy. Although these animals approached food first and ate it immediately, indicating an increased need for it, they did not gain weight.

Animals with signs of cachexia showed a statistically significant 22% decrease in BMI compared to control animals from the same colony (Figs. 1, 2).

3.2 MicroRNA expression analysis

3.2.1 Naked mole rat microRNA annotation

After filtering by quality and length, microRNA sequences from the liver, kidney, heart, and skeletal muscle of the naked mole rat were obtained. The pool of all identified sequences was annotated according to their human orthologs from the Mirbase database. This is the first naked mole rat microRNA database (Suppl. Tab. 1). 162 new sequences with 90–100% identity to human orthologs have been described. Moreover, no human analogues were found for 22 naked mole rat small RNA sequences. Based on this, it is logical to assume that the naked mole rat is characterized by additional specific regulation of gene expression. Its adaptive significance can be further clarified by studying the microRNA spectrum of species genetically and ecologically close to the naked mole rat (*Mus musculus, Cavia porcellus, Ellobius talpinus, Cryptomys damarensis*).

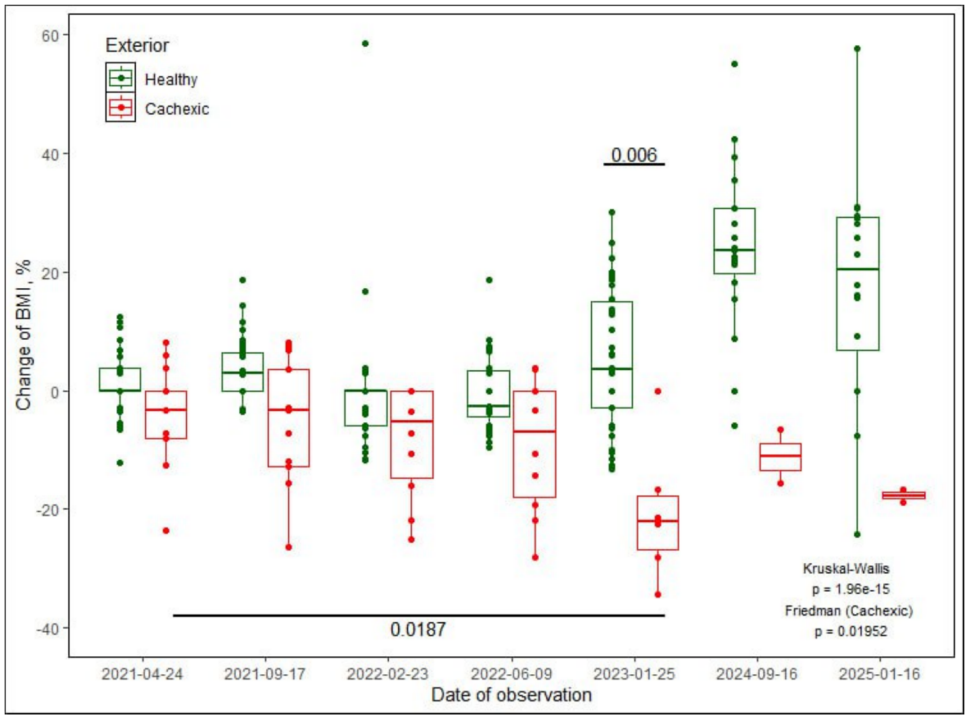


Fig. 1 Graph shows the changing of body mass index of health naked mole rats (green boxplot) and animals with cachexia (red boxplot) for 3 years (Health animal n = 9, Cachexic animal = 9). Numbers (significant p-value) with bars shows significant group differences

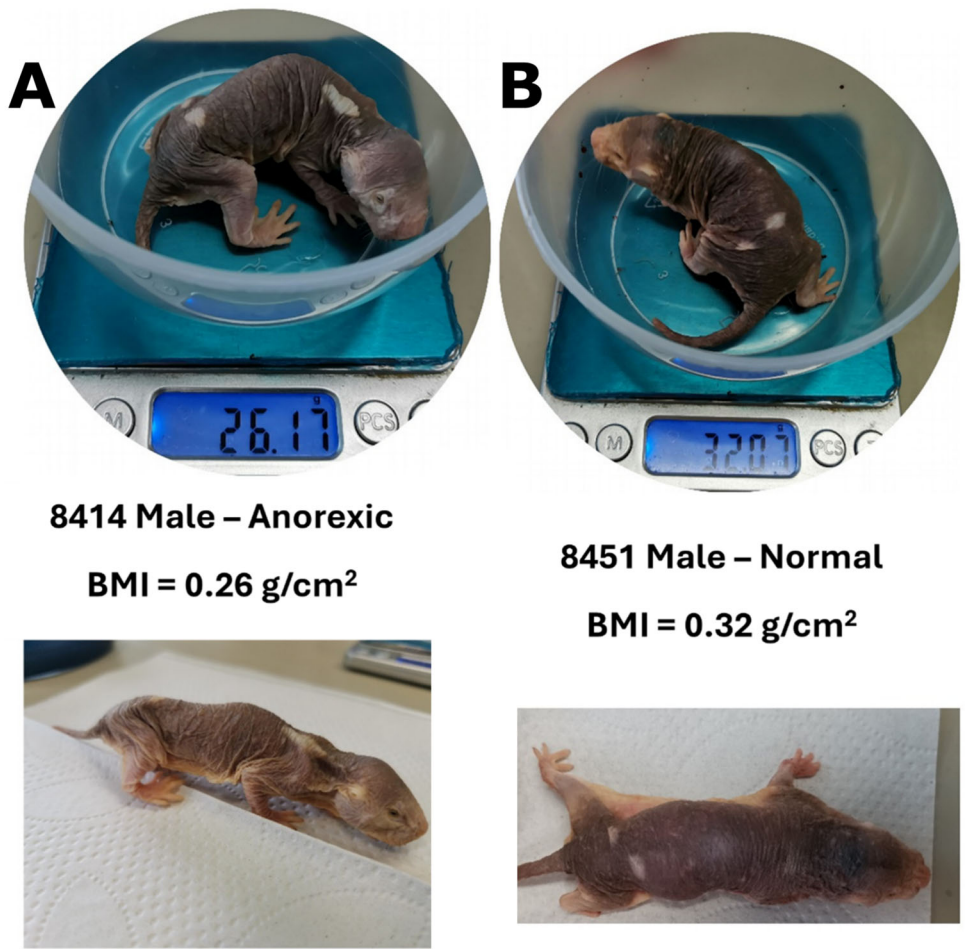


Fig. 2 **A** Phenotype of health naked mole rat. **B** Phenotype of naked mole rat with idiopathic cachexia

3.2.2 MicroRNA analysis

After filtering the sequences obtained by sequencing based on length and quality, miRNA sequences from the liver, kidney, heart, and skeletal muscle of naked mole rats were obtained. A target analysis was performed, and miRNAs identified in the liver, kidney, heart, and skeletal muscle were enriched using GO, KEGG, Reactome, and Wikipathways. Analysis of the signaling pathways and processes associated with the identified miRNAs and their target genes revealed multiple, multidirectional pathways that determine a wide range of cellular and even extracellular functions involved in normal physiology and spontaneous idiopathic cachexia in naked mole rats (Table 1).

4 Discussion

The phenotype and BMI changes of the cachectic animals revealed that, for some unknown reason, these animals were unable to gain weight. They exhibited the same feeding behavior as other animals and were even more aggressive. As workers, they did not carry food to the nest but consumed it immediately in the feeding compartment. This observation can be explained by the fact that the animals had significantly higher energy expenditure at rest than control animals, as observed in hyperthyroid mice [12]. Based on these data, we conclude that cachectic naked mole rats belonged to the active 'subcaste', i.e., workers or dispersers [13]. These abnormal animals had low body surface temperatures, which correlated with bursts of activity, and were often found in the clay chamber.

Heterothermy was previously confirmed in four naked mole rat workers in chronic laboratory experiments [14]. Naked mole rats are known to be heterothermic animals, and their temperature decreases when they leave their nest [15]. This would allow us to identify active animals, such as workers and dispersers [13]. Kovalzon et al. implanted ECOLOGGERS (miniature autonomous temperature and locomotor activity sensors, EMBI RESEARCH LLC, Novosibirsk) into naked mole rats (2 males, 2 females) intraperitoneally through a small incision (under light isoflurane anesthesia). During the circadian period of activity, their body temperature decreased by 3–5 °C, and at rest it raised again to 33–34 °C. These temperature fluctuations were independent of the presence or absence of lighting in the chamber (Fig. 3). Long-term continuous EEG recordings conducted on four other individual worker subjects revealed a number of unusual characteristics of paradoxical (REM) sleep (PS), not previously described in any mammalian species. The proportion of PS was unusually high for an adult mammal (up to 50% of the total sleep time); PS episodes could precede episodes of orthodox (REM) sleep. In the EEG, PS episodes were characterized by an unusually powerful synchronized rhythm with a frequency of 11–15 Hz, which was twice as high as the theta rhythm of other rodents studied so far [16] (Fig. 4). For this article, we decided to conduct a meta-analysis of the first mentioned work by Kovalzon [14], with his consent.

Animals in a single colony showed synergistic changes in core body temperature and activity, which were represented as acceleration force (Fig. 5). Coincident peaks were observed, but the changes in these parameters were antagonistic. Based on the results (Table 1), we concluded that the animals were in a resting state 69% of their time. They had low core body temperature and high activity 25% and 23% of the time, respectively. Coincidence of low temperature and high activity was observed in 17% of all data points, which accounted for 68% and 74% of the time of low temperature and high activity, respectively. The changes in temperature and activity were significant (Fig. 5A, B; Table 2). The temperature during the active state (coincident with the peak of activity) was 30.9 °C (Fig. 6C), in the resting state it was 33.6 °C (Fig. 6A), and the acceleration force reached 0.12 g in the active state compared to 0.02 g in the resting state. Occasionally temperature and acceleration peaks did not coincide (Fig. 6C, D), and their parameters might differ slightly but significantly. Thus, a decrease in temperature in response to increased activity is a common feature of naked mole rats, and the physiology of these animals is determined by their own biological rhythm.

However, it was a mystery why animals became cachexic, performing normal duties in the colony. Taking into account data from mRNA analysis, we supposed that cachexic naked mole rats were in state near of homeostasis decompensation, because there were upregulation of metabolic and other processes in their organs and at the same time downregulation of the PI3K/AKT network, signaling pathway responsible for cell survival, upregulation of metabolic processes, vascular growth, etc. [17, 18]. Particularly the PI3K/AKT network take part in muscle tropism, and downregulation of this pathway led to skeletal muscle atrophy in mice [19], that correlated with cachexic naked mole rat appearance. So, these animals experienced some kind of stress, which was absent in natural conditions, but it existed in captivity. We assumed that this factor turned out to be hyperoxia. In nature naked mole rats' burrows hypoxic environment is maintained around 8–15% O_2 [7]. While in captivity where O_2 concentration is 21%, these animals are stressed by hyperoxia observed as accumulation of lipid peroxidation products even in young age, comparing with mice [10]. There have also been studies examining the effects of hyperoxia on the organs of mice and humans. In the liver, hyperoxia has been associated with cirrhosis and fibrosis, where damage was enhanced by transforming growth factor-β (TGFβ) [20]. This is consistent with our

Table 1 The analysis of the signaling pathways and processes related to the identified microRNAs

Organ	#category	Term ID	Term description	Observed gene count	Background gene count	Strength	False discovery rate
Muscle	GO Process	GO:0010604	Positive regulation of macromolecule metabolic process	247	3533	0.49	1.39E−65
	GO Process	GO:0051240	Positive regulation of multicellular organismal process	168	1505	0.69	1.64E−65
	GO Process	GO:0051173	Positive regulation of nitrogen compound metabolic process	230	3166	0.51	2.37E−62
	GO Process	GO:0031325	Positive regulation of cellular metabolic process	228	3114	0.51	3.19E−62
	GO Process	GO:0051094	Positive regulation of developmental process	149	1332	0.69	4.53E−57
	Reactome	HSA-199418	Negative regulation of the PI3K/AKT network	21	113	0.92	1.33E−10
Kidney	GO Process	GO:0010604	Positive regulation of macromolecule metabolic process	115	3533	0.54	9.85E−36
	GO Process	GO:0009893	Positive regulation of metabolic process	117	3847	0.51	4.28E−34
	GO Process	GO:0051173	Positive regulation of nitrogen compound metabolic process	105	3166	0.55	2E−32

Table 1 (continued)

Organ	#category	Term ID	Term description	Observed gene count	Background gene count	Strength	False discovery rate
	GO Process	GO:0031325	Positive regulation of cellular metabolic process	102	3114	0.54	1.11E−30
	GO Process	GO:0051247	Positive regulation of protein metabolic process	65	1512	0.66	3.14E−23
	GO Process	GO:0009891	Positive regulation of biosynthetic process	75	2080	0.58	4.46E−23
	GO Process	GO:0031328	Positive regulation of cellular biosynthetic process	74	2041	0.59	7.23E−23
	GO Process	GO:0010557	Positive regulation of macromolecule biosynthetic process	71	1935	0.59	4.78E−22
	GO Process	GO:0051240	Positive regulation of multicellular organismal process	63	1505	0.65	6.65E−22
Liver	GO Process	GO:0051173	Positive regulation of nitrogen compound metabolic process	278	3166	0.45	1.88E−60
	GO Process	GO:0031325	Positive regulation of cellular metabolic process	274	3114	0.45	1.77E−59
	GO Process	GO:0010605	Negative regulation of macromolecule metabolic process	253	2760	0.47	8.66E−57

Table 1 (continued)

Organ	#category	Term ID	Term description	Observed gene count	Background gene count	Strength	False discovery rate
	GO Process	GO:0051240	Positive regulation of multicellular organismal process	184	1505	0.6	7.63E−55
	Reactome	HSA-199418	Negative regulation of the PI3K/AKT network	22	113	0.8	5.01E−09
Heart	GO Process	GO:0051173	Positive regulation of nitrogen compound metabolic process	330	3166	0.46	9.15E−73
	GO Process	GO:0051094	Positive regulation of developmental process	208	1332	0.63	7.82E−67
	GO Process	GO:0008284	Positive regulation of cell population proliferation	175	945	0.71	1.34E−64
	GO Process	GO:0051240	Positive regulation of multicellular organismal process	216	1505	0.6	6.33E−64
	GO Process	GO:0043066	Negative regulation of apoptotic process	167	891	0.71	4.97E−62
	GO Process	GO:0043069	Negative regulation of programmed cell death	168	911	0.71	1.5E−61
	Reactome	HSA-199418	Negative regulation of the PI3K/AKT network	26	113	0.8	1.13E−10

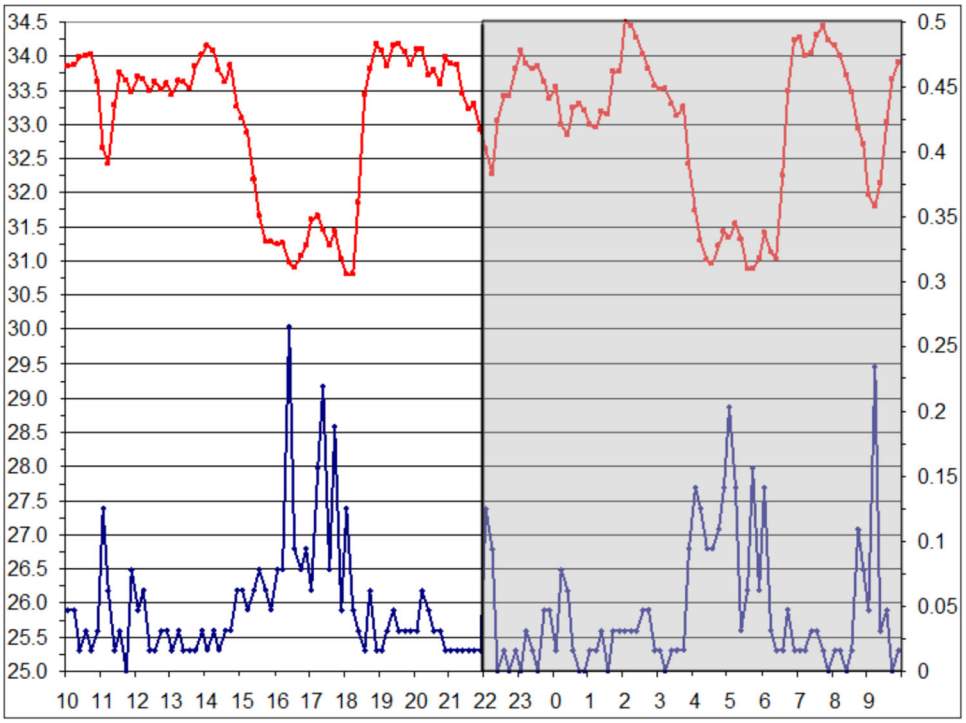


Fig. 3 Representative fragment of a 24-h record of body temperature (upper red curve, left ordinate, centigrade) and motor activity (lower blue curve, right ordinate, δG) in a naked mole rat (#8496). The abscissa axis shows the time of day. The shaded part is the dark period in the chamber. A clear reciprocity in the dynamics of both functions is visible [14]

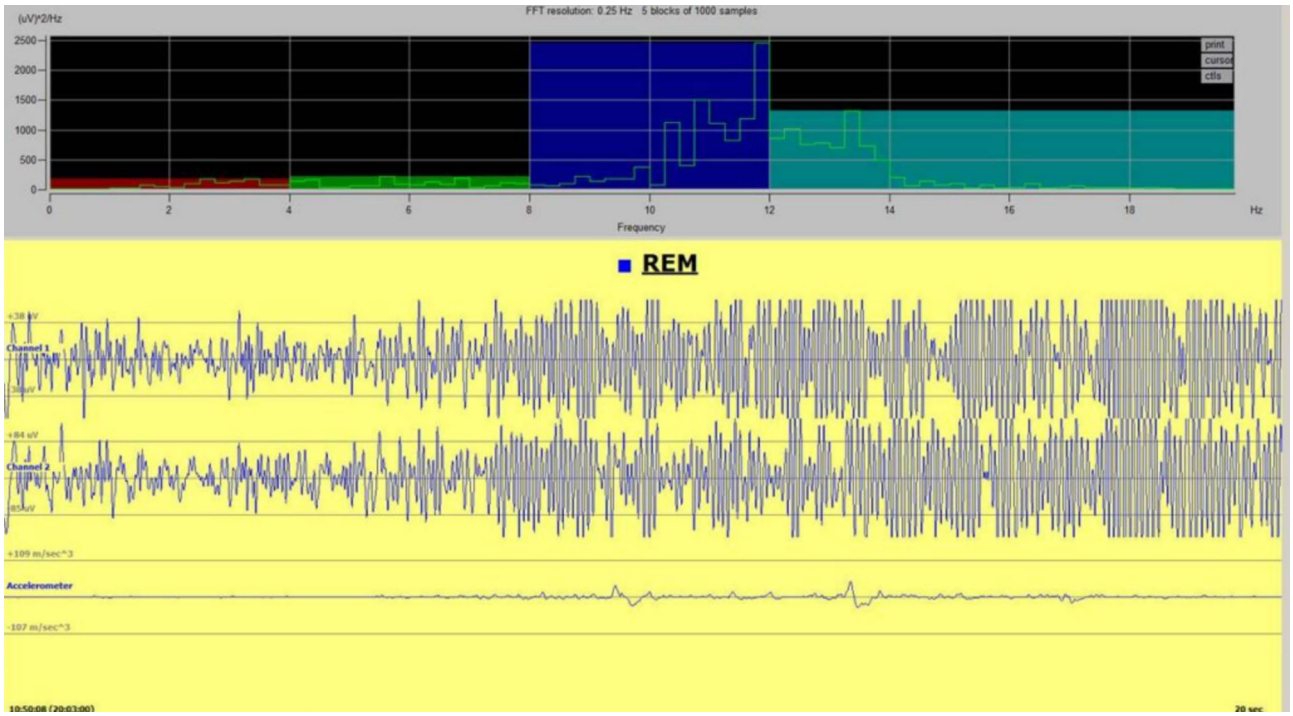


Fig. 4 20-s fragment of EEG recording of a naked mole rat (#8447). EEG from the frontal and parietal cortex on channels 1 and 2. The graph at the top is the spectral analysis of the 1st channel. The transition from ordinary sleep (on the left side of the recording) to high-voltage synchronized activity with a frequency of 12 Hz, characteristic of paradoxical sleep, against the background of a complete absence of activity on the accelerometer is visible [16]

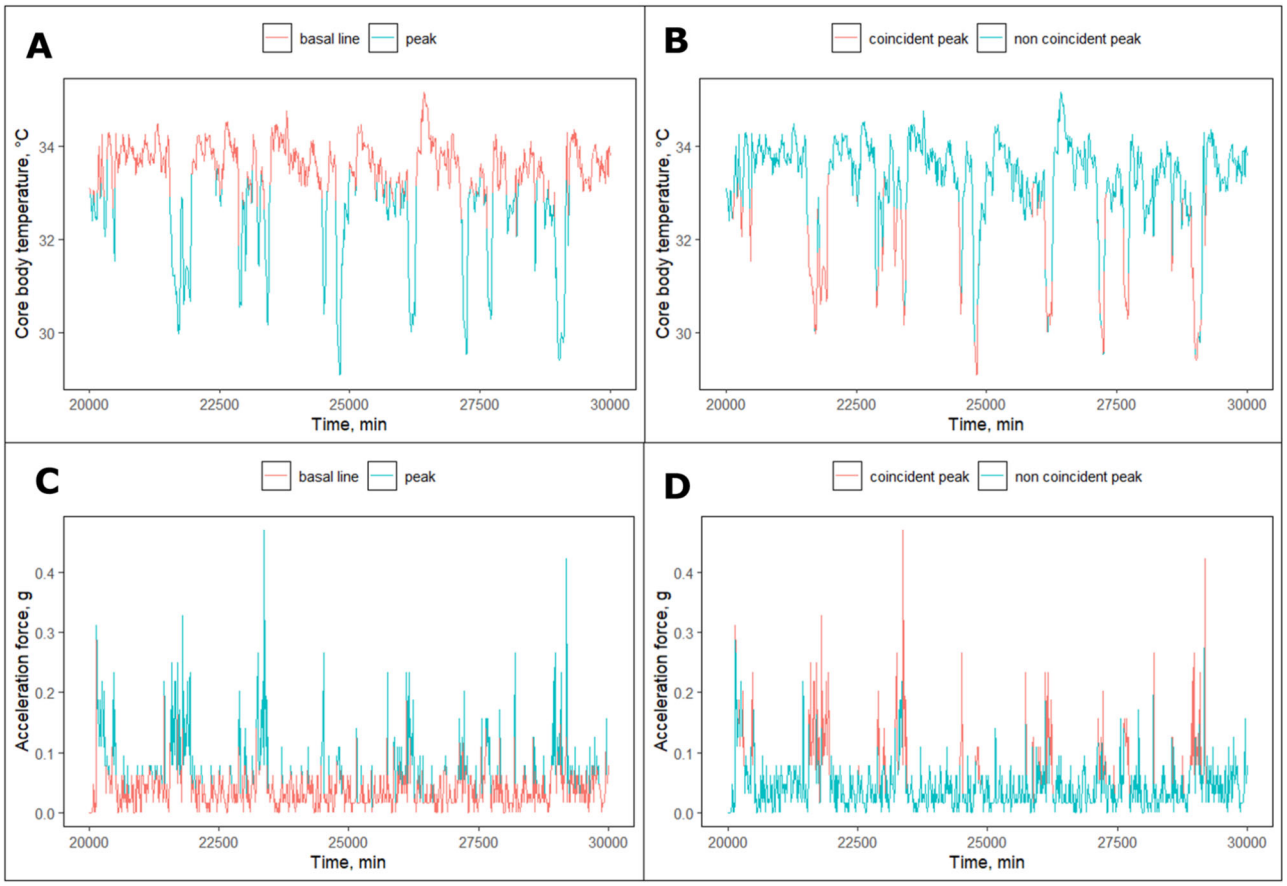


Fig. 5 A part of recording of core body temperature and activity of a naked mole rat (#8439). **A** Core body temperature peak and basal line determination, **B** core body temperature peak coincidence with acceleration force peak, **C** acceleration force peak and basal line determination, **D** acceleration force peak coincidence with core body temperature peak

results, since TGFβ activates protein phosphatase 2a (PP2a), which dephosphorylates AKT, inhibiting its function [21].

In mice, cardiac hyperoxia caused hypertrophy and a decrease in cardiac output and heart rate [22], whereas in humans with coronary artery disease it caused regional deoxygenation and deterioration of myocardial function [23]. The decrease in heart rate and cardiac output is consistent with the condition of naked mole rats in captivity with high oxygen levels, as naked mole rats have lower heart rates and cardiac function than mice [24] and do not change with age [25]. Although it should be noted that at the same time hyperoxia and even hyperbaric conditions can lead to beneficial effects in patients with acute coronary syndrome [26]. Thus, the naked mole rat may be more vulnerable to hyperoxia than other species.

In summary, cachexia in naked mole rats can be caused by increased physical activity in hyperoxic conditions, with workers and dispersers—that is, animals with high physical activity—being most susceptible. Increased physical activity in the colony should be avoided unless hypoxia (8–15%) is achieved. Hyperoxia can lead to liver damage due to oxidative stress, which can lead to a reduction in lifespan. This effect suggests a possible vulnerability of naked mole rats to elevated oxygen levels in the environment, which is explained by their physiological predisposition to life in oxygen-deficient conditions. However, why the resting metabolic rate in these animals increases even after the provoking factor has been removed remains a mystery. This may be a consequence of the irreversible effects of prolonged oxidative stress on the body, leading to disruption of cellular regulation and integrative systems. Further research on these animals is needed to clarify this issue.

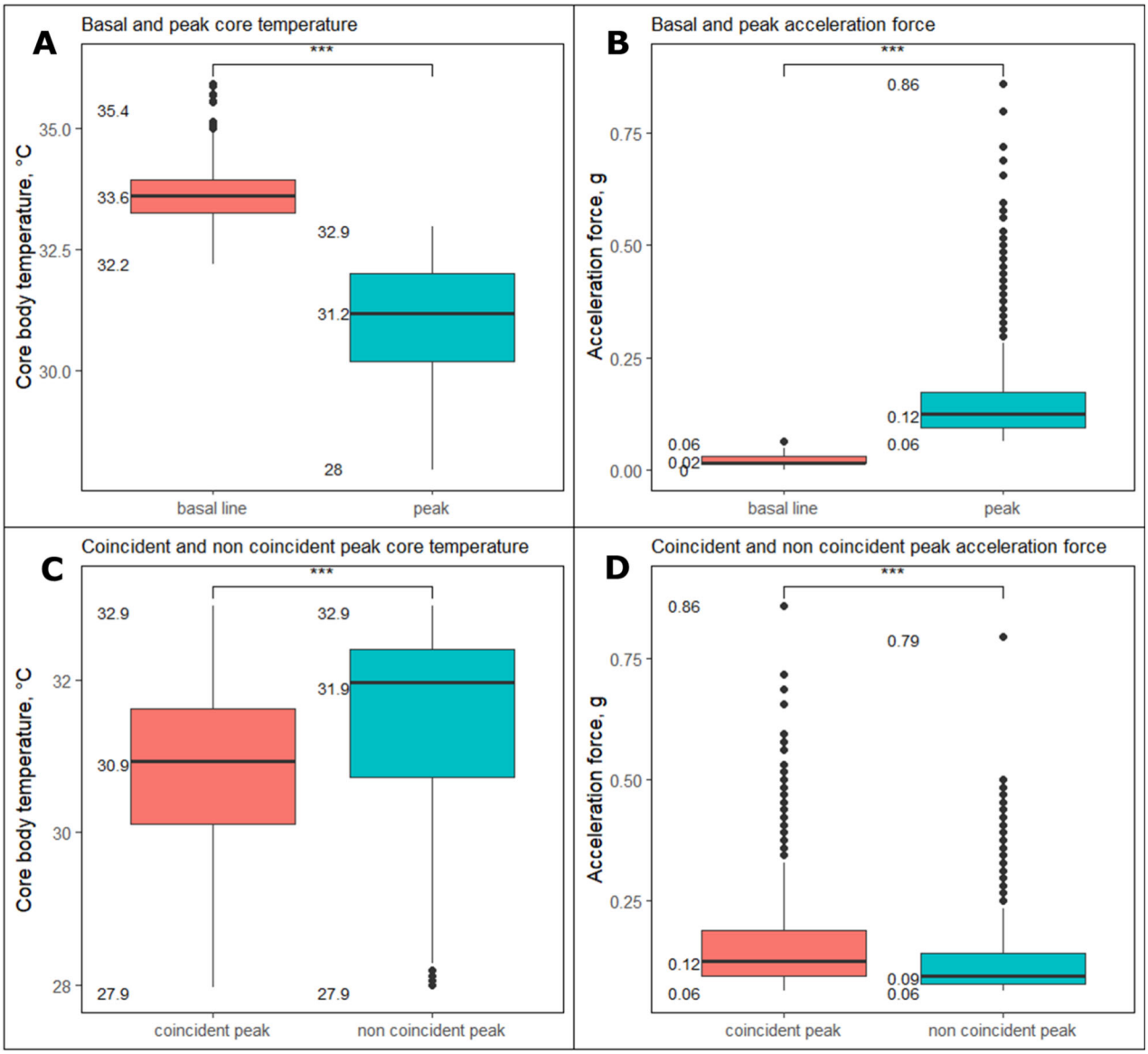


Fig. 6 The changes of core body temperature and activity. Student's T-test. ***p-value < 0.001. **A** Difference in core body temperature between peak and basal line, **B** difference in acceleration force between peak and basal line, **C** difference in core body temperature between coincident and non coincident peaks, **D** difference in acceleration force between coincident and non coincident peaks. Numbers near boxplots represent maximal, median and minimal value of distribution

Table 2 Frequency table of acceleration force and temperature point type

		Acceleration force point type			
		Absolute values		Relative values	
		Basal line	Peak	Basal line	Peak
Temperature point type	Basal line	14219	1312	0.69	0.06
	Peak	1741	3436	0.08	0.17

Pearson's Chi-squared test with Yates' continuity correction p-value $< 2.2e^{-16}$

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1140/epjs/s11734-025-02100-1.

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Author contributions

Conceptualization MV, VK; data curation MA, VK, OA, AR, IM, MB; formal analysis MA, VK, MB, IM, CE, AR; investigation VK, MB, IM, OA, AS; methodology VK, IM, OA, VM, ES; supervision MV, VK; writing—original draft MA; writing—review and editing VK, MV.

Data availability The datasets generated during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors declare no competing interests.

Animal ethics Local Ethics Committee of the A.N. Belozersky Research Institute of Physical Chemistry and Biology of Moscow State University Protocol 2/20 dated 11/16/2022.

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