Unique neurophysiologic characteristics of the longest-living rodent: the naked mole rats

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Heterocephalus glaber or the naked mole rats(NMRs) belongs to the genus nude moles of the Bathyergidae family, which is the only kind of temperature changing mammal with true sociality in the world and shares 93% genetic homology with humans[1]. Long-term subterranean burrowing living has led to NMRs gradually evolved a series of physiological characteristics that are significantly different from mammals living on the ground, such as vitamin D deficiency[2], sensory organs degeneration and extreme hypoxia tolerance[3, 4]. Despite the harsh living environment, NMRs are extremely long-lived. Their average lifespan is 5-7 times that of laboratorial mice of the same size, up to 30 years[5]. These physiological characteristics of NMRs giving them a good applicable prospect when studying neurological related diseases such as pain, ischemic stroke, and Alzheimer's disease(AD). Here, we have reviewed the studies published on the neurophysiological characteristics of NMRs to provide reference for future research.
Keywords: naked mole rats, pain resistance, Alzheimer's disease

1.Social hierarchy dependent neurogenesis.

NMRs colony has a large population, which can accommodate up to 300 individuals, and has a highly organized social hierarchy system[6]. In one colony, there is usually only one female and 1-3 males responsible for

reproduction. The reproductive capacity of other individuals is repressed, and they are mainly responsible for work such as cave maintenance, group protection, foraging, and raising offspring[7]. The female NMR responsible for reproduction is usually the largest individual in the group. Distinguishing from the gradually degenerating productive ability with age in most mammals, the "queen of NMRs" can keep breeding till death, and the older the stronger of its reproductive ability[5]. Oosthuizen et al found that the social hierarchy of NMRs is the most significant regulator of neurogenesis. Interestingly, the neurogenetic ability of NMRs is significantly negatively correlated with their social status, that is, the“queen”has the lowest neurogenesis ability, and the "worker NMRs" have the highest neurogenesis ability[8], this is independent of the effect of sex hormones[9]. By analyzing the density of corticotropin-releasing factor(CRF) receptors in the brain of NMRs between different genders and different social hierarchies, Beery et al found that the subtype CRF1 content had a significant social status dependence, while the subtype CRF2 content not only had a social hierarchy dependence but also had a gender difference[10]. The results of Hathaway's research suggested that oxytocin (OT) also played an important role in regulating the social behavior of NMRs[11]. The aforementioned researches indicate that the neurophysiological characteristics of NMRs are associated with their social behavior, and neuroendocrine may play an important regulatory role in it.

2. Strong tolerance to pain.

Previous studies indicated that NMRs have a strong tolerance for pain. Nociceptive stimuli causing pain in animals can be divided into mechanical (such as tail clamp and cauterization) and chemical (such as capsaicin and acid). The peripheral nerves of most vertebrates are sensitive to these two types of nociceptive stimuli. However, NMRs are only sensitive to mechanical stimuli rather than chemical stimuli, indicating that they have unique neurophysiological characteristics in the mechanism of pain perception[12, 13]. Park et al believed that this might be related to the lack of substance P and calcitonin gene-related peptides(CGRP) in c-type unmyelinated fibers of the eyes, upper respiratory tract, and skin of NMRs. The aforementioned two neuropeptides are necessary signaling molecules for c-type unmyelinated fibers to induce pain[14]. Besides, unlike c-fibers of laboratory mice, which connected only with superficial posterior horn neurons, nearly half of the NMRs c-fibers were connected to neurons in the deep posterior horn of the spinal cord, the physiological significance for this phenomenon is

unclear[12]. In mammals, unmyelinated c-fibers promote wound healing by secreting substance P and CGRP to induce vasoconstriction, cell proliferation, and immune response at the site of injury. Therefore, due to the lack of the two substances mentioned above, the wound healing of NMR was slow, indicating that the loss of neuropeptide increase the adaptability of NMR to nociceptive stimuli but reduce their wound healing and immune response-ability.

Many studies have proved that the tolerance of pain in NMR could be contributed to multiple mechanisms. In the study of hyperalgesia induced by nerve growth factor (NGF) in NMRs, Omerbašić et al found that although NMRs had fully functional TRPV1 channels to mediate NGF induced hyperalgesia, the efficiency for TRPV1 activation initiated by NGF combining to its receptor TrkA was very low, which may be associated with the substitution of amino acids 1 and 3 in the TrkA kinase region[15]. J rgensen et al found that the muscarinoid acetylcholine receptor subtype was involved in the pain tolerance mechanism of NMRs, which could be reversed by atropine[16]. Acid-sensing ion channels (ASICs) are homologous trimers or heterotrimers formed by the activation of extracellular protons, which are involved in a variety of pathophysiological processes in mammals, including pain and anxiety. Schuhmacher et al observed that the ASIC3 of NMRs is a non-functional homologous isomer, which may be the reason for its insensitivity to acid stimulation[17]. Using RNA sequencing technology, Eigenbrod tracked the sequence variation of the transduction channel during pain tolerance process in NMRs, they found that the transient receptor potential channel (TRPA1) and voltage-gated sodium channel Na (v) 1.7 were increased, indicating that NMRs could suppress nociceptive sensation by increasing variant ion channels expression[18]. This researches suggested that the tolerance to pain of NMRs is the result of a combination of multiple mechanisms, which is conducive to the adaptation of NMRs to the harsh living environment in the burrow.

3.Adjustable body temperature and basal metabolic rate.

Compared with laboratorial mice, basal metabolic rate (BMR) of NMRs was lower. NMRs have larger thermally neutral zone with higher thermal conductance than mice, and the mass-specific metabolic rate was about 75% of that in mice. The crowded and humid environment of the burrows prevents evaporation and convection, so keeping the metabolic rate low allows NMRs to better adapt to its surroundings. When the ambient temperature was 28℃, the metabolic rate of NMRs was the highest,

which was equivalent to that of mice at 4℃. When the ambient temperature below 28℃, the body temperature and the metabolic rate of NMRs living alone in dry air began to decrease, and they could endure for several hours even when their body temperature dropped to 12℃[2]. Like other rodents, NMRs rely on the brown adipose tissue between the shoulder blades for heat production, rather than on the adrenaline-dependent shivering heat production[19]. Low BMR was associated with low thyroid hormone levels in NMRs. Under laboratory conditions, when the room temperature dropped from 30℃ to 25℃, the thyroxine level of NMRs began to increase, accompanied by an increase in ingestion. However, even when the room temperature was kept at 25℃, thyroxine level in NMRs was still lower than that in mice[20]. In addition, the reduction of BMR and body temperature is one of the physiological mechanisms by which naked mole rats can effectively resist hypoxia[21]. When NMRs were exposed to a gradually increasing hypoxia environment, their BMR, body temperature, and activity decreased[3], which was associated to the decrease of mitochondrial electron transport chain flow and $H^{(+)}$ gradient in a balanced and regulated manner[22]. These findings suggest that NMRs can not only adapt to the subterranean environment by maintaining low BMR and body temperature, but also resist extreme hypoxia by further lowering BMR, the underlying mechanism is related to the regulation of mitochondrial function by thyroxine.

4.Unique sensory organs.

Long time of subterranean living has led to a distinguishing evolution for the sensory organs in NMRs compared with that of mice. First, dark surroundings severely degrade the visual function of NMRs. Compared with mice, NMRs have small eyes with typical ocular structures such as the cornea, lens, and retina. The cross-sectional area and fiber density of the optic nerve in NMRs is about 10% and 50% of that in gerbil, respectively, and they can only perceive light and dark changes around[4]. However, unlike other mammals, retinal ganglion cells(RGCs) in NMRs can survive with its strong regenerating ability of axonal when optic nerve damage happened. Second, NMRs have a poor high-frequency hearing with a low hearing threshold[23], but they are very sensitive to close range hearing. Within the group NMRs apply a complex auditory-

voice communication system containing at least 17 different sounds to communicate information[2]. NMRs have a acute sense for smell and a well developed olfactory cortex, which may be a compensating mechanism for their visual degradation[24]. NMRs can accomplish a variety of health-related tasks by smelling, such as foraging and defense[25]. In rodents, the vomeronasal organ at the bottom of the nasal cavity responds to pheromones and plays a key role in regulating social and sexual behavior, such as reproductive repression[26]. Interestingly, the vomeronasal organ in NMRs is very small at birth and does not grow with age[27], suggesting that the pheromone-mediated regulation of reproductive repression does not apply to NMRs[28].

Tactile feeling is the most important composition for the sensory system of NMRs. It have established that the tactile feeling cortex was major part of the sensory cortex in the brain of NMRs, which even extends to the traditional visual cortex areas[29]. Distinguished from other terricolous mammals, NMRs have thin, almost bare skin, with only 80 sensory vibrissae arranged in a grid mode on the entire body. Anatomical researches suggested that NMRs have fewer but more robust skin vibrissae than other rodents, by which they can accomplish orientating. Crish et al found that deflection of even one single vibrissae of NMRs can initiate an extremely reliable and accurate orientating, indicating that vibrissae is special tactile sensitive point for NMRs, with a function that be similar with facial whiskers in mice[30].

5.Hypoxia tolerance.

To decrease O_2 consumption, subterranean mammals often live alone or in small groups. In sharp contrast, the population size of NMRs is huge and they often crowded together, leading to local O_2 depletion and CO_2 accumulation, forming an anoxic living environment[31]. Living in such environment, NMRs have gradually evolved strong tolerance to hypoxia[32]. Even when the ambient oxygen concentration decreased to 3%, NMRs remained active and maintained normal physiological function[3]. Compared with laboratorial mice, when the oxygen content in the environment gradually decreased, the synaptic integrity for brain neurons of NMRs could be maintained for a longer period, even after 30 minutes of exposure to the oxygen-free condition[33].

Reducing metabolic rate is an important strategy for NMRs to adapt to the anoxic living environment[34]. When exposed to the anoxic environment, the breathing rate, heart rate, and metabolic rate of NMRs decreased significantly[35]. The decrease of metabolic rate can reduce the

oxygen consumption of naked mole rats and maintain the balance between “supply and demand”of oxygen in cells. Besides, the enhancement of oxygen utilization coefficient for cells is also an important mechanism of hypoxia tolerance in NMRs. When exposed to chronic and persistent hypoxia, the oxygen uptaking capacity of NMRs neurons could be increased to three times than that of laboratorial mice[36]. Brain developmental retardation may be another important strategy for NMRs to resist hypoxia. In the brain of adult mammals, there is a phenomenon of paired impulse facilitation, that is, when a pair of stimuli are used to cause two impulses in rapid succession, the amplitude of the second impulse will increase significantly. Park et al found that this phenomenon did not exist in the brains of rat pups or NMRs, indicating that NMRs have developmental retardation[37]. Some scholars believe that it is precisely because of developmental retardation that NMRs have a hypoxic tolerance similar to that of newborn rats[2].

The molecular mechanisms of hypoxia tolerance in NMRs are very complex. Expressing high levels of glucose transporter 5(GLUT5) in the brain of NMRs are considered as the molecular characteristics of fructose metabolism. Under hypoxia conditions, the anaerobic metabolism of NMRs is driven by fructose, which can accumulates in NMRs brain and be metabolized to lactate. This fructose-driven glycolysis avoids the feedback inhibition of glycolysis by phosphofructokinase and improves cell survival[35]. When exposed to hypoxia, the intracellular calcium levels of mammalian brain slices gradually increased, leading to cell death. Reducing the accumulation of hypoxia-induced intracellular calcium is associated with hypoxia tolerance in animals[32]. Compared with mice, the intracellular calcium accumulation induced by hypoxia in the CA1 region of the hippocampus of NMRs is significantly reduced, accompanied by the enhancing ability for hypoxia tolerance[38]. The mechanism of reducing intracellular calcium accumulation in NMRs brain may be related to the highly expressed GluN2D subtype of NMDA receptor(a type of calcium ion channel)[39, 40]. Neurons in NMRs can also enhance hypoxia tolerance ability by reducing excitatory glutamate receptor currents and increasing inhibitory currents of GABA aminobutyric acid receptor[41]. In addition, when hypoxemia occurs, the content of vascular endothelial growth factor (VEGF) is significantly increasing in circulation of NMRs as well as c-fos expression in the brain. Both VEGF and c-fos are crucial neuroprotective factors[42].

6.Anti-aging brain.

The average lifespan of NMRs is 5-7 times longer than that of

laboratorial mice with same size, up to 30 years[5]. This may be attributed to the developmental retardation in NMRs. Pan et al have found that adult NMRs retained many physiological characteristics of immature individuals, such as GluN2D and MHC-βexpression, reduced intracellular Ca^{2+} accumulation in hypoxic conditions, and stopped growth of vomeronasal organ after birth[43]. There are lots of pathological signs in mammalian brains with age, including degraded neurogenesis and synaptic plasticity, decreased contents of signaling molecules (neurotrophic factor, neurotransmitters and cytokines, and steroids, etc.), enhanced oxidative stress and damaged vasculature. Nevertheless, NMRs showed no such pathological changes throughout their lifetime[44]. Content of nerve growth factor(NGF) in the brain of NMRs does not decrease with age and is significantly higher than that in mice with same size[2]. Miranda et al found that although NMRs born with more developed brain than mice, their brain were developing slowly after birth, taking four times than mice to get mature[45]. These results indicate that developmental retardation gives NMRs an extraordinarily long life.

Latest studies have shed new light on the mechanisms of anti-aging for NMRs. By studying the gene-splicing pattern in the brain of NMRs, Lee et al found that after transient unstable in early life, the alternative splicing(AS) pattern of brain related genes in adult NMRs remained remarkably stable for at least 20 years, enabling NMRs to maintain long-term health[46]. When studied the mitochondrion of NMRs, Vyssokikh et al found that the membrane potential of the NMRs mitochondrion was in a state of mild depolarization, which could effectively resist the damage of reactive oxygen species(ROS)[47]. Miranda et al found that the content of phosphorylated tau protein was the highest in neurons during the stage of brain development and then decreasing with age, nevertheless, it was still significantly higher than that in transgenic mice over-expressing mutant human tau protein. Intriguingly, in contrast to pathologically depositing in the midbrain of transgenic mice, tau protein in the brain of NMRs is located in axons with normal function[48]. In another study for amyloid β(Aβ) in the brain of NMRs, Edrey et al found similar results to the aforementioned study. Namely, the content of Aβ in the brain of adult NMRs is identical to that in 3xtg-AD mice (a transgenic model mouse of AD) but no extracellular amyloid plaques formed. Besides, the content of Aβ in the brain of NMRs did not increase with age[49]. These two studies indicate that the nervous system degeneration in NMRs is not evident with age, and further study for the underlying mechanism may help the prevention and treatment for AD.

Conclusion

In summary, NMRs have unique neurophysiological characteristics, including social hierarchy dependent neurogenesis, resistance to hypoxia, pain and aging. The underlying mechanism of these characteristics is very complex, involving metabolism, ion channels, mitochondrial function, and protein expression. The unique neurophysiological characteristics of NMRs may be attributed to multiple mechanisms. The study of the neurophysiological characteristics of NMRs is of great significance for the prevention and treatment for pain and neurodegenerative diseases.

Data accessiblity

Data have not been archived because this article does not contain data.

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