Naked Mole-Rats: Blind, Naked, and Feeling No Pain

Brigitte M Browe*, Emily N Vice*, Thomas J Park#

* These authors contributed equally

Corresponding author

University of Illinois at Chicago

Laboratory of Integrative Neuroscience

Department of Biological Sciences

840 West Taylor St.

Chicago, Illinois, 60607

United States of America

Corresponding Author:
Thomas Park
phone 312 413 3020
FAX 312 996 2805
E-mail tpark@uic.edu

Individual and address to whom correspondence concerning manuscript should be sent:
Thomas Park
University of Illinois at Chicago
Laboratory of Integrative Neuroscience
Department of Biological Sciences
840 West Taylor St.
Chicago, Illinois, 60607
United States of America

Running title: Extreme Adaptations of the Naked Mole-Rat

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/ar.23996

Abstract

Around the world and across taxa, subterranean mammals show remarkable convergent evolution in morphology (e.g. reduced external ears, small eyes, shortened limbs and tails). This is true of sensory systems as well (e.g. loss of object vision and high frequency hearing). The naked mole-rat (*Heterocephalus glaber*) displays these typical subterranean features, but also has unusual characteristics even among subterranean mammals. Naked mole-rats are cold-blooded, completely furless, very long-lived (> 30 years), and eusocial (like termites). They also live in large colonies, which is very unusual for subterraneans. Their cortical organization has reduced area for visual processing, utilizing 30% more cortex for tactile processing. They are extremely tolerant to oxygen deprivation, and can recover from 18 minutes of anoxia. Their pain pathway is reduced and they feel no pain from acidosis. They are the only rodent tested to date whose pheromone-detecting vomeronasal organ shows no postnatal growth. These features may be a result of this species' "extreme subterranean lifestyle" that combines living underground and living in large colonies. Many respiring animals cramped together in unventilated burrows elevates CO_2 levels, high enough to cause acidosis pain, and depletes O_2 concentrations low enough to kill other mammals. The naked mole-rat may be an extreme model of adaptation to subterranean life and provides insights into the complex interplay of evolutionary adaptations to the constraints of subterranean living.

Introduction

Fossorial mammals, having found their niche in subterranean ecotopes, are faced with an array of physiological challenges that drive specific adaptations (for a thorough review see: Bennett and Faulkes, 2000, Jarvis and Bennet, 1991). Life underground lacks certain

environmental properties of terrestrial life such as regular exposure to sunlight, physiologically "normal" air composition, fluctuations in ambient temperature and normal propagation of sound. Subterranean ecosystems are often resource poor with scarce food. The animals that live in these conditions have developed ways to meet these challenges head on. The African mole-rat family Bathyergidae has successfully adapted to a life underground. Evidence of the Bathyergidae family can be traced back at least 40-50 million years ago (Faulkes et al., 2004; Pickford et al., 2008). It is composed of 12 genera and about 30 species. Though they are classified in the Rodentia order, there has been some debate over their suborder classification due to the unique skull morphology and head musculature of the African mole-rat family that disallows classical distinction (Honeycutt et al., 1991).

Heterocephalus glaber or the African naked mole-rat is a member of the Bathyergidae family and is the only species in its genus. Naked mole-rats are found in the Horn of Africa in areas of Ethiopia, Kenya and Somalia. The climate in these areas is hot and dry with an average annual rainfall of 600mm (Burda, 2001). While members of the Bathyergidae family are universally subterranean (Jarvis and Bennett, 1991), their underground habitat consists of burrows of varying complexity. The burrow systems of naked mole-rat are comprised of multiple nests, toilet chambers, food storage chambers and deep tunnels for defensive retreat (Jarvis and Bennett, 1991, Brett, 1991). These burrows are dynamic and remodeled to regulate ambient temperature, moisture and to expand foraging range. The length of the burrow directly correlates to the biomass of the colony (Jarvis and Bennett, 1991) and is modulated to meet the needs of the colony.

Naked mole-rat burrows are almost completely removed from the elements of the surface. The ambient temperature of the burrows is relatively constant with little fluctuation

throughout the day and throughout the year (Brett, 1991). In the instance of temperature fluctuation, naked mole-rats transition to different lamina within the system to arrive at a physiologically favorable ambient temperature (their preferred temperature being ~30 degrees C (Begall et al., 2015)). This is especially important because naked mole-rats do not thermoregulate; they are poikilothermic (Buffenstein and Yahav, 1991). However, this has not impeded naked mole-rats' ability to thrive as they have little need to self-generate heat in this habitat and, consequently, they are able to conserve much needed energy for their great foraging need. In addition to being poikilothermic, naked mole-rats are also unusual in that they have a low resting metabolic rate (Buffenstein and Yahav, 1991) they are very long lived (Buffenstein, 2008), and they are very resistant to cancer (Liang et al, 2010; Tian et al., 2013).

Adult naked mole-rats range in size from 25 grams (**Figure 1**), which is similar to a mouse, to 60 grams, which is similar to a small rat. Their size is dependent on factors such as food availability, colony size, and soil hardness which accounts for the broad variability in body mass (Jarvis and Bennett, 1991). Like other subterraneans, their body is cylindrical, and like other African mole-rats, naked mole-rats have enlarged incisors, which grow from above and below the lips (e.g the incisors are located permanently exterior to the oral cavity, see Figure 1c in Catania and Remple, 2002), and only 2-3 molar teeth in each jaw (Catania and Remple, 2002). Like many subterraneans, naked mole-rat have tiny eyes and no external ear pinnae (Mason, 2016). Their skin is loose and wrinkled, which allows them to easily maneuver in the tight spaces of their tunnel habitat.

Within the family Bathyergidae there is a full spectrum of sociality ranging from a solitary lifestyle to the highest degree of sociality (Bennett and Faulks, 2000). Naked mole-rat colonies have a highly organized eusocial division of labor similar to social insects like termites.

The social hierarchy of naked mole-rats is established by age and weight; the oldest and heaviest leading in rank. The dominant female is typically the largest female in a colony and is the exclusive breeding female. The dominant female is often referred to as the queen, a nomenclature used in the description of eusocial insects (Jarvis, 1981). The queen suppresses reproductive maturation in her colony mates except for two or three males (Jarvis, 1981). The queen inhibits the circulation of sex hormones in subordinate females though physical intimidation instead of through pheromones in urine like other rodents (Margulis, 1995; Dengler-Crish and Catania, 2007). As the queen is the only female to reproduce, this generates a highly inbred population within the colony.

High sociality and large colony size in a subterranean environment may have led to unusual traits in somatosensation, the vomeronasal organ, and responses to hypoxia and pain. The main aim of the present manuscript is to review these extreme, putative adaptations. This is important because it reveals how evolution can result in novel solutions to extreme environmental problems.

Somatosensory Adaptations

Naked mole-rats have very poor visual function (Hetling et al., 2005) and sound localization ability (Heffner and Heffner, 1993). Instead they rely heavily on their tactile senses to navigate their complex tunnel systems. They are also likely to be sensitive to vibrations (Mason and Narins, 2010). Seki and colleagues (2013) have shown that there is prenatal development of the optic nerve; however, this nerve, and additional markers for the visual system, decrease after birth leaving the eye fully developed but very small for a rodent (Hetling et al, 2005). Also, the brain's vision centers are diminished to the point where only broad shapes

and variations of light are detectable by the adult (Hetling et al, 2005; Xiao et al. 2006). Naked mole-rats may also retain a diminished circadian input (Ooshuizen, 2010) though their pineal gland is significantly reduced compared to mice (Kim et al, 2011; Quay, 1981). In conjunction with a reduction in visual cortex, the somatosensory cortex appears to utilize an increased cortical volume to increase tactile representation. This is confirmed by the substantial changes in cortical structures (Catania and Remple, 2002; Seki et al., 2013). The primary somatosensory cortex (S1 region) of the naked mole-rat is increased by up to 51% (Xiao et al., 2006). This caudal expansion projects into what is expected to be visual cortex in rats and mice.

Naked mole-rats have well developed facial whiskers (Crish et al., 2003) and a weak (compared to mice) barrel pattern in somatosensory cortex representing the largest facial whiskers (Park et al., 2007). However, much of the increase in the S1 region can be considered a direct effect of the increased representation of tactile body vibrissae (Xiao, 2006) also known as somatic vibrissae (Park et al., 2003). *Naked* mole-rats lack fur, as the word "naked" suggests, but naked mole-rats do have regularly arranged whisker-like vibrissae on their bodies, which are well innervated, similar to guard hairs of furred species (Park et al., 2003). There are approximately 40 vibrissae on each side of the body, organized into a grid-like pattern (**Figure 2A,B**). The body vibrissae are arranged topographically into a sensory array, and stimulation of a given vibrissae elicits an orienting response to the point of stimulation (**Figure 2C,D**) (Crish et al., 2003). The structure and innervation of the body vibrissae follicles resemble those of exceptionally large guard hairs in other mammals (Park et al., 2003). Mechanically stimulating a single vibrissa causes a robust turn of the naked mole-rat's head to bring the snout to the point of contact. Importantly, when two ipsilateral vibrissae are stimulated simultaneously, the animal orients to a location midway between the two stimulated vibrissae ("averaging"; Crish et al.,

2006). On the contrary, when two hairs are stimulated on opposite sides of the body, the animal responds with a full response to one of the stimulated hairs and not the other ("winner take all"; Crish et al., 2006). These findings are important because they indicate that, within a hemifield, the naked mole-rat nervous system performs computations (averaging) of multiple points of contact. It is also noteworthy that naked mole-rats, like many subterraneans, routinely locomote backwards (Lacey et al., 1991), particularly when vibrissae on the tail are stimulated (Crish et al., 2003).

The incisors are also overrepresented in the somatosensory cortex of the naked mole-rat, indicating that they are well innervated (Catania and Remple, 2002). Like most of the other African mole-rats, naked mole-rats construct their tunnels by digging with their oversized incisors and they use their teeth to carry young, food, and debris (Jarvis and Bennett, 1991 Catania and Remple, 2002). The incisors are very conspicuous because the lips meet behind the incisors (**Figure 1**), allowing the animals to close their lips behind the incisors while burrowing. Nearly 25% of the total musculature of a naked mole-rat is dedicated to the jaws, including separate muscles that give naked mole-rat the ability to independently move their incisors (Catania and Remple, 2002). The cortical area associated with this large amount of muscle corresponds to 30% of the somatosensory cortex (in the lateral region), and 10% of the neocortex is associated with motor control of the jaw and incisors (Catania and Remple, 2002). While representation of the facial regions within S1 are not as distinct in naked mole-rat as in mice and rats, a barrel pattern can still be distinguished (Henry et al., 2006). Like other rodents, naked mole-rat have a dense localization of cells in layer IV of the somatosensory cortex that correspond to body parts used for burrowing- in particular, their incisors and forelimbs (Henry et al., 2006). Conversely, the secondary connections for the incisors remain very local and have

little connection to the anterior cortex, instead exhibiting reciprocal connections within the somatosensory cortex (Henry and Catania, 2006).

Olfaction and the Vomeronasal Organ

Mammals have two olfactory systems, the main and the accessory. In the main olfactory pathway odorous molecules travel to the posterior nasal cavity where they are detected by the olfactory receptors of the olfactory neuroepithelium (Buck and Axel, 1991). Olfactory receptors (ORs) are seven-transmembrane G-protein coupled receptors encoded by the OR-gene superfamily, the largest gene family in the vertebrate genome (Buck and Axel, 1991; Lancet and Ben-Arie, 1993). The extent of the functional OR-gene repertoire varies significantly among vertebrates as a function of evolutionary pressure on olfactory reliance (Stathopoulos et al., 2014) with a direct association between functional OR diversity and olfactory acuity (Kishida, 2008). Animals that rely heavily on olfaction for fitness-related tasks express a more extensive functional-OR repertoire compared to animals who rely on other sensory modalities – such as humans who rely predominately on trichromatic vision (Niimura and Nei, 2006).

African mole-rats live in dark underground burrows which has resulted in a family-wide reduction in visual acuity (Němec et al., 2008). This loss of visual abilities is compensated for by enhanced olfactory sensitivity with positive selection for functional OR-gene diversity (Stathopoulos et al., 2014). The entire family also expresses a degree of encephalization comparable to that of terrestrial rodents, which are generally characterized as having an acute sense of smell (Kruska and Seffen, 2009). Some Bathyergidae species even exhibit larger olfactory regions compared to *Rattus norvegicus* or the common rat (Kruska and Steffen, 2009), most likely to be a compensation for reduction of visual function.

The naked mole-rat is no exception to the enhanced olfaction demonstrated by its family. The naked mole-rat exhibits well-developed olfactory structures in the brain (Hill et al., 1957; Pilleri, 1960) despite having the smallest brain within the family (Pirlot, 1990; Kruska and Steffen, 2009). The naked mole-rat relies on odors for many fitness-related tasks such as recruitment of colony members toward a food source (Judd and Sherman, 1996) as well as xenophobic behavior (O'Riain and Jarvis, 1997). The naked mole-rat demonstrates the structural, molecular and behavioral markers for acute olfactory sensitivity.

As mentioned previously, naked mole-rats exhibit xenophobic behaviors by aggressing towards non-colony members. Interestingly, this individual recognition is not mediated through pheromones as it is in other rodents (O'Riain and Jarvis, 1995). Pheromones are described as molecules released by an individual that elicit a physiological and behavioral response in another individual of the same species (Tirindelli et al., 2009). In many mammals, pheromonal detection is mediated through the accessory system's chemosensory structure - the vomeronasal organ (VNO) which is embedded at the base of the nasal septum and lined with neuroepithelium in rodents (Meredith and O'Connell, 1979).

There is rapid peri- and postnatal proliferation of the sensory neurons of the VNO in mice, rats and other mammals (Weiler et al., 1999; Wilson and Raisman, 1980). Interestingly, the naked mole-rat shows no post-natal growth of the VNO (**Figure 3**) (mean vomeronasal neuroepithelium VNNE volumes were 0.012 mm^3(± 0.005 mm3) for subadults and 0.015 mm^3 (± 0.007 mm^3) for adults, $p>.05$, Smith et al., 2007). The VNO is essential for mediating sociosexual cues in many vertebrates, however naked mole-rats appear not to rely on pheromones to relay this information (Faulkes and Abbott, 1993; Judd and Sherman, 1996; O'Riain and Jarvis, 1997). Apparently, the naked mole-rat demonstrates behavior-mediated

sexual suppression instead of relying on pheromone-based urinary signals like rats, mice, and other rodents. The dominant breeding female in a naked mole-rat colony imposes her status through physical intimidation which inhibits the circulation of sex hormones (Margulis et al., 1995). It is thought that this divergence from the Rodentia "norm" is a result of the naked mole-rat's eusocial social structure eliminating the need for pheromonal-based sexual suppression (Smith et al., 2007). Overall, the naked mole-rat exhibits acute main olfaction structurally and molecularly; while the accessory pathway is extremely reduced. It is possible that pheromonal detection is occurring through the main olfactory pathway as is thought to occur in humans and some other vertebrates (e.g. Frasnelli et al., 2011).

Hypoxia Tolerance

Most subterranean mammals are solitary or live in small groups which avoids depleting the available supply of oxygen (O_2). Naked mole-rats, on the contrary, are extremely social and live in colonies of as many as 300 animals. Also, they tend to spend much of their time sleeping or huddling together in deep nesting chambers. This leads to local depletion of O_2 and accumulation of carbon dioxide (CO_2) at a greater extent than that experienced by other subterraneans (Faulkes and Bennett, 2013). Naked mole-rats display dramatic adaptations to survive and even thrive in these conditions that would be deadly to most mammals.

Intrinsic brain tolerance

In mammals, the brain is particularly susceptible to injury from oxygen deprivation (Russell, 1964). However, naked mole-rats show extreme intrinsic brain tolerance to hypoxia and anoxia (Larson and Park, 2009; Larson et al., 2014). Hippocampal brain slices from naked mole-

rats can recover from O_2 concentrations that rapidly kill slices from mice, including 0% O_2. **Figure 4** shows the effects of low concentrations of O_2 on field excitatory post-synaptic potentials (fEPSPs) measured in slices from naked mole-rats and mice before, during, and after exposure to hypoxia (**Figure 4A,B**). Summary data show that on average, slices from naked mole-rats have less of an acute loss of function during hypoxia (**Figure 4C**) and a better recovery rate after hypoxia (**Figure 4D**) compared to slices from mice. Under nominal 0% O_2, slices from naked mole-rats continue to function much longer than slices from mice (**Figure 4E**). This is true at two different temperatures: at 35 degrees C, close to the physiological temperature of mice, and at 30 degrees C, the naked mole-rats' preferred temperature **(Figure 4F).**

When slices from rats and mice are exposed to hypoxia, there is a progressive increase in intracellular calcium levels that rapidly leads to calcium toxicity and cell death. Reduction of hypoxia-induced intracellular calcium accumulation is associated with hypoxia tolerance in many hypoxia-tolerant animals (Larson et al., 2014; Peterson, 2012a). The hippocampal CA1 region of slices from naked mole-rats shows a significant attenuation of hypoxia-induced intracellular calcium accumulation compared to mice (Peterson, 2012b). The composition of ionotropic glutamatergic NMDA receptors in naked mole-rat brain cells may play an important role in attenuating intracellular calcium accumulation during hypoxic assault. NMDA receptors are calcium channels. The efficacy of NMDA subunits to open the channel can contribute to toxicity levels within the cells, with high subunit efficacy leading to cell death but low efficacy contributing to cell protection during hypoxia (Lee et al., 1991). NMDA receptors with GluN2D subunits exhibit the lowest opening efficacy of all of the NMDA subunits, to a sufficient level to protect against hypoxic injury (Bickler et al., 2003). The number of NMDA receptors that express the GluN2D subunit decreases greatly in mice and rats shortly after birth, reducing the

hypoxia resistance that is seen during fetal development (Laurie et al., 1997). In contrast, naked mole-rats retain a large proportion of NMDA receptors with GluN2D: 66% in naked mole-rats versus 10% in mice (Peterson, 2012b).

In vivo tolerance

In vivo experiments show that intact naked mole-rats tolerate severe hypoxia (5% O2) and anoxia (0% O_2) much longer than mice (**Figure 5A,B**) (Park et al., 2017). Naked mole-rats can recover from 18 minutes of exposure to 0% O_2, more than 18 times longer than mice (**Figure 5C**). During exposure to 0% O_2, naked mole-rats show a robust decrease in respiration and heart rates (**Figure 5D,E**) reminiscent of a suspended animation-like state (Park et al., 2017).

Metabolic rates decrease during hypoxia; however, because naked mole-rats are poikilothermic, they do not show significant changes in their body temperature (Park et al., 2017). Reducing metabolism during oxygen deprivation allows naked mole-rats to conserve cellular oxygen, possibly to the point of matching O_2 need with O_2 availability. Naked mole-rats show a 50% reduction in acute hypoxic ventilatory response (HVR) and hypoxic metabolic rate during acute hypoxia. Naked mole-rats exhibit metabolic O_2 extraction at 3x that of normoxic animals but no change in ventilator plasticity following chronic sustained hypoxia (Chung et al., 2016). Gamma aminobutyric acid (GABA) signaling contributes to breathing patterns and ventilatory and metabolic responses to hypoxia – specifically GABA antagonism increases breathing frequency and decreases tidal volume in naked mole-rats but does the opposite in mice – altering breathing patterns but not ventilation or metabolism (Chung et al., 2016). Moreover, the ventilation response has been shown to be regulated by adenosine receptors; activation of these receptors blocks the reduction in ventilation (Pamenter et al., 2014).

Hypoxic conditions also have serious consequences for the heart. In mice and rats extended exposure to low oxygen can lead to myocardial lesions, edema, and capillary injury (Meneely, 1974). Additionally, it is important to maintain high functioning status during hypoxic assault to maintain oxygen flow to other body parts (Abe et al., 2017). When exposed to anoxia in an atmosphere chamber, the heart rate of a naked mole-rat greatly decreases in the first 1-2 minutes and stabilizes at approximately 25% of baseline rate until oxygen is reintroduced (Park et al., 2017). Isolated heart experiments show an intrinsic ability for the organ to continue to beat during anoxia as well as to completely recover left ventricular developed pressure (LVDP) while mice can only recover to about 65% (Park et al., 2017). Anatomically, naked mole-rat hearts maintain similar cellular structure to mice, in terms of striation patterns and sarcomere architecture, but overall the size of the naked mole-rat heart is statistically larger by an average of 60mg. Furthermore, the cardiomyocyte cross-sectional area averages 40 mm^2 and diastolic wall thickness is 0.1mm^2 greater in naked mole-rat compared to mice. Naked mole-rats predominantly express MHC-β in their ventricles unlike mice who express very little MHC-β in their hearts after birth (Grimes et al., 2014). MHC-β is considered the fetal analog of MHC- α, the predominant protein in adult mice (Katsumata et al., 2017). Phosphorylation of cardiac troponin T and myosin light chain in naked mole-rats is half that of mice. Interestingly, naked mole-rats express both cardiac and skeletal troponin in their ventricular tissue, which, like the MHC-β expression, appears to be retention of neonatal traits as an adaptation for hypoxia tolerance (Grimes et al., 2017).

Fructose metabolism

Naked mole-rats show a high expression of the GLUT5 transporter in organs that do not usually express much GLUT5 (e.g. heart and brain) (Park et al., 2017). This adaptation is paramount to one of the most unusual adaptations to hypoxia that has been identified in a mammal. The GLUT5 transporter specifically transports fructose across cell membranes, and in the naked mole-rat it actively transports fructose into brain and heart cells. During anoxia, naked mole-rats maintain stable glucose levels because they are able to utilize fructose in an oxygen-independent manner to maintain function (Park et al., 2017). Experiments with hippocampal brain slices and isolated hearts suggest that these organs can switch from glucose metabolism to fructose metabolism (**Figure 6**). **Figure 6A** shows a schematic of the hippocampal slice preparation and example fEPSP traces on the left, and average fEPSPs amplitudes over time from mouse and naked mole-rat slices on the right. When bath glucose was switched to fructose, slices from naked mole-rats maintained greater functionality and much better recovery compared to slices from mice. **Figure 6B** shows that isolated hearts from naked mole-rats maintain close to baseline function during two serial episodes when bath glucose was switched to fructose. In contrast hearts from mice showed a substantial decline in function, particularly during the second episode.

Nociception

The preceding section focused on adaptations associated with living in a chronically low O_2 environment. However, naked mole-rats also are faced with living in chronically high CO_2 concentrations that would cause tissue acidosis with associated pain, as well as pulmonary edema in other mammals (Park et al., 2017). Naked mole-rats show a much higher threshold before

avoiding CO_2 compared to mice (**Figure 7A,B**), suggesting that they are less sensitive to CO_2-induced pain (Park et al., 2017). Also, naked mole-rats are insensitive to pain from breathing acetic acid fumes (LaVinka and Park, 2012). Experiments to measure pulmonary edema from breathing high concentrations of CO_2 revealed that naked mole-rats do not get pulmonary edema, even from very high concentrations of CO_2 (**Figure 7C**) (Park et al., 2017).

In the upper respiratory tract, acidosis activates sensory neurons in the pain pathway. In the lungs, acidosis activates similar sensory neurons, which trigger a neurogenic inflammatory response leading to edema. Protection from CO_2-induced pain and pulmonary edema in naked mole-rats is associated with a sequence variant in the naked mole-rat voltage-gated sodium channel Nav1.7 (Smith et al., 2011). Nav1.7 channels normally propagate action potentials along the axons of peripheral receptor cells that respond to CO_2-induced acidosis. However, the variant in naked mole-rat Nav1.7 causes it to be inhibited in the presence of acid.

Interestingly, naked mole-rats are also insensitive to pain in the nasal cavity from other (non-acid) chemical pain stimuli, including capsaicin solution (the active ingredient in chili peppers), and fumes from ammonia (LaVinka et al., 2009; LaVinka and Park, 2012). Chemical pain is transduced by a specific population of peripheral pain fibers: they are unmyelinated, small caliber fibers called polymodal pain fibers or C fibers. The term polymodal derives from the ability of these fibers to respond to multiple modes of pain: chemical, inflammatory, heat, and mechanical (Beitel and Dubner, 1976). The gene variant in Nav1.7 should be specific for affecting acid pain but not pain from capsaicin and ammonia. However, the C fibers in naked mole-rats also lack the neurotransmitter, Substance P (Park et al., 2003; Park et al., 2008), which is associated with signaling chemical and inflammatory pain (Cao et al., 1998). This may explain at least part of the naked mole-rats' insensitivity to non-acid painful chemicals.

The insensitivity to acid and other chemical pain stimuli described above for naked mole-rats is not restricted to the upper respiratory tract. Rather, insensitivity to chemical pain is found in the skin of the entire body. This makes sense for acid insensitivity because the gene variant for the Nav1.7 channel should make this channel inhibited by acid in all peripheral pain fibers (Smith et al., 2011; Liu et al., 2014). This also makes sense for Substance P-related insensitivity to non-acid chemical pain stimuli if lack of Substance P is a result of dysregulation of promoter genes specific to the peripheral nervous system, as suggested by the genetic analysis of Kim et al (2011).

Consistent with an altered Nav1.7 channel and lack of peripheral Substance P, naked mole-rats demonstrate a very distinct pattern of pain behaviors. **Figure 8** shows the results of a battery of pain tests on naked mole-rats and, for comparison, laboratory mice (Park et al., 2008). Naked mole-rats do not differ from mice in their response to acute mechanical pain (pinch) or acute heat, associated more with A-delta pain fibers, not C pain fibers (**Figure 8A**). However, naked mole-rats show virtually no response to paw injections of the chemical pain stimuli, capsaicin and acidic saline, associated with C fibers (**Figure 8B**). In tests of inflammatory pain, naked mole-rats do show sensitization to pressure but not heat during inflammation from complete Freund's adjuvant (CFA) (**Figure 8C,D**). They also show no sensitization from application of topical capsaicin or injection of nerve growth factor (NGF) (**Figure 8E,F**). Finally, naked mole-rats show a very reduced response to paw injection of 1% formalin solution (**Figure 8G**).

Interestingly, a sensitization response to topical capsaicin can be rescued in naked mole-rats using a gene therapy approach (Park et al., 2008). **Figure 9** shows foot withdrawal latencies before and after application of capsaicin. One foot was treated with a recombinant herpes virus

carrying the gene for Substance P, (preprotachykinin, PPT). The virus-treated foot showed a much faster withdrawal after treatment, indicative of sensitization, compared to the control foot.

It is noteworthy that naked mole-rats show no sensitization to heat after treatment with NGF or the inflammatory agents CFA and capsaicin. Sensitization to heat, called thermal hyperalgesia is mediated by the NGF receptor TrkA, which sensitizes the transient receptor potential vanilloid-1 (TRPV1) receptors. A recent study has shown that the naked mole-rat TrkA receptor has a small mutation that reduces functionality of the receptor for NGF signaling and abolishes thermal hyperalgesia while retaining other important functions of TrkA (Omerbašić et al., 2016).

Delayed or arrested development

Extreme adaptations are pushed by niche habitats to enable an animal to thrive, even in the most unusual places. For naked mole-rats, that habitat is deep underground, and they thrive in an environment that is actually quite familiar to most mammalian species during a distinct time in their life. Their warm, humid, and oxygen deprived habitat is very similar to the start of every mammal's life, in a womb. Aptly, many of the adaptations that naked mole-rats display appear to be associated with slowed development and retention of fetal traits. These include retention of GluN2D and MHC-β, greatly reduced Ca2+ accumulation during hypoxia, and the lack of VNO growth past pn1. Coincidentally, Substance P (lacking in the peripheral nerves of naked mole-rats) also mediates the VNO's vascular pump. Lack of Substance P may disable the pump, which would degrade the functionality of the VNO. In the respiratory system, pulmonary neuroepithelial bodies retain neonate characteristics (Pan et al., 2014), possibly allowing naked mole-rats to respond to ambient gas concentrations as do neonates. Further evidence for the

naked mole-rat's delayed maturation can be seen in the development of the central nervous system. Naked mole-rat brains continue to grow for months after birth, reaching 90% of their final volume at 3 months of age, and neuronal markers of maturation continue to be unstable for twice that time (Orr, 2016). Neoteny may also contribute to the naked mole-rats' longevity. It has also been shown that synapse distribution and firing patterns do not mature to the same level as that of mice – even after 1 year of age – and that appears related to naked mole-rats' retention of structural plasticity (Penz et al., 2015). This suggests that cellular reorganization instead of neurogenesis is the means of neuroadaptive longevity and is a potential means for naked mole-rats to adapt to the added challenges of living underground under chronic low O_2/high CO_2 conditions.

Conclusions

The naked mole-rat's large colony size and extreme social structure have been integral to their successful foraging in an environment with extremely dispersed food resources. However, this unusual lifestyle comes with major challenges: chronically low O_2 concentrations and chronically high CO_2 concentrations. We postulate that these extreme environmental pressures have driven extreme adaptations in the naked mole-rat for coping with otherwise deadly oxygen deprivation and tissue acidosis.

Acknowledgments

We are grateful for funding from a UIC College of Liberal Arts and Sciences Award for Faculty of Sciences and the National Science Foundation (grant 1655494). We are also grateful for the extremely helpful suggestions of two anonymous reviewers and the journal editors.

Literature Cited

Abe H, Semba H, Takeda N. 2017. The roles of hypoxia signaling in the pathogenesis of cardiovascular diseases. J Atheroscler Thromb 24:884-894.

Begall S, Berendes M, Schielke C, Henning Y, Laghanke M, Scharff A, van Daele P, Burda H. 2015. Temperature preferences of African mole-rats (family Bathyergidae). J Therm Biol 53:15-22.

Beitel RE, Dubner R. 1976. Response of unmyelinated (C) polymodal nociceptors to thermal stimuli applied to monkey's face. J Neurophysiol 39:1160-75.

Bennett NC, Faulkes CG. 2000. African Mole-Rats: Ecology and Eusociality. Cambridge: Cambridge University Press.

Bickler PE, Fahlman CS, Taylor DM. 2003. Oxygen sensitivity of NMDA receptors: Relationship to NR2 subunit composition and hypoxia tolerance of neonatal neurons. Neuroscience 118:25-35.

Brett RA. 1991. The ecology of naked mole-rat colonies: Burrowing, food, and limiting factors. In The Biology of the Naked Mole-Rat. Sherman PW, Jarvis JUM, Alexander RD, eds. Princeton: Princeton University Press 137-184.

Buck L, Axel, R. 1991. A novel multigene family may encode odorant receptors: a molecular basis for odor recognition. Cell 65: 175-187.

Buffenstein R. 2008. Negligible senescence in the longest living rodent, the naked mole rat: insights from a successfully aging species. J. Comp. Physiol. 178:439-445.

Buffenstein R, Yahav S. 1991. Is the naked mole-rat Heterocephalus glaber an endothermic yet poikilothermic mammal? J Therm Biol 16:227-232.

Burda H. 2001. Determinants of the distribution and radiation of African mole-rats (Bathyergidae, Rodentia): ecology or geography? In African Small Mammals / Petits Mammifères Africains, Proceedings of the 8th International Symposium on African Small Mammals / Communications Présentées au 8e Symposium International sur les Petits Mammifères Africains. Denys C, Granjon L, and Poulet A (eds.) 263-277.

Cao YQ, Mantyh PW, Carlson EJ, Gillespie AM, Epstein CJ, Basbaum AI. 1998. Primary afferent tachykinins are required to experience moderate to intense pain. Nature 392:390-394.

Catania KC, Remple MS. 2002. Somatosensory cortex dominated by the representation of teeth in the naked mole-rat brain. Proc Natl Acad of Sci 99:5692-5697.

Chung D, Dzal YA, Seow A, Milsom WK, Pamenter ME. 2016. Naked mole-rats exhibit metabolic but not ventilatory plasticity following chronic sustained hypoxia. Proc Biol Sci 283:20160216.

Crish SD, Rice FL, Park TJ, Comer CM. 2003. Somatosensory organization and behavior in naked mole-rats I: Vibrissa-like body hairs comprise a sensory array that mediates orientation to tactile stimuli. Brain Behav Evol 62:141-151.

Crish SD, Dengler-Crish CM, Comer CM. 2006. Population coding strategies and involvement of the superior colliculus in the tactile orienting behavior of naked mole-rats. Neuroscience 139:1461-1466.

Dengler-Crish CM, Catania KC. 2007. Phenotypic plasticity in female naked mole-rats after removal from reproductive suppression. J Exp Biol 210:4351-8.

Faulkes CG, Abbott DH. 1993. Evidence that primer pheromones do not cause social suppression of reproduction in male and female naked mole-rats (Heterocephalus glaber). J Reprod Fertil 99:225-230.

Faulkes CG, Bennett NC. 2013. Plasticity and constraints on social evolution in African mole-rats: Ultimate and proximate factors. Philos Trans R Soc Lond B Biol Sci 368: 20120347.

Faulkes CG, Verheyen E, Verheyen W, Jarvis, JUM, Bennett NC. 2004. Phylogeographical patterns of genetic divergence and speciation in African mole-rats (family: Bathyergidae). Mol Ecol 13:613-629.

Frasnelli J, Lundström JN, Boyle JA, Katsarkas A, Jones-Gotman M. 2011. The vomeronasal organ is not involved in the perception of endogenous odors. Hum Brain Mapp 32:450-460.

Grimes KM, Voorhees A, Chiao YA, Han HC, Lindsey ML, Buffenstein R. 2014. Cardiac function of the naked mole-rat: Ecophysiological responses to working underground. Am J Physiol Heart Circ Physiol 306:H730–H737.

Grimes KM, Barefield DY, Kumar M, McNamara JW, Weintraub ST, de Tombe PP, Sadayappan S, Buffenstein R. 2017. The naked mole-rat exhibits an unusual cardiac myofilament protein profile providing new insights into heart function of this naturally subterranean rodent. Pflugers Arch. 469: 1603-1613.

Heffner RS, Heffner HE. 1993. Degenerate hearing and sound localization in naked mole-rats (Heterocephalus glaber), with an overview of central auditory structures. J Comp Neurol 331:418-433.

Henry EC, Catania KC. 2006. Cortical, callosal, and thalamic connections from primary somatosensory cortex in the naked mole-rat (Heterocephalus glaber), with special emphasis on the connectivity of the incisor representation. Anat Rec A Discov Mol Cell Evol Biol 288:626-45.

Henry EC, Remple MS, O'Riain MJ, Catania KC. 2006. Organization of somatosensory cortical areas in the naked mole-rat (Heterocephalus glaber). J Comp Neurol 495:434-52.

Hetling JR, Baig-Silva MS, Comer CM, Pardue MT, Samaan DY, Qtaishat NM, Pepperberg DR, Park TJ. 2005. Features of visual function in the naked mole-rat (Heterocephalus glaber). J Comp Physiol A Neuroethol Sens Neural Behav Physiol 191:317-30.

Hill WCO, Porter A, Bloom RT, Seago J, Southwick, MD. 1957. Field and laboratory studies of the naked mole rat, Heterocephalus glaber. Proc Zool Soc Lond 128:455-514.

Honeycutt RL, Allard MW, Edwards SV, Schlitter DA. 1991. Systematics and evolution of the family Bathyergidae. In The Biology of the Naked Mole-Rat. Sherman PW, Jarvis JUM, Alexander RD, eds. Princeton: Princeton University Press: 45-65.

Jarvis JUM. 1981. Eusociality in a mammal: Cooperative breeding in naked mole-rat colonies Science 212:571-573.

Jarvis JUM, Bennett NC. 1991.Ecology and behavior of the family Bathyergidae. In The Biology of the Naked Mole-Rat. Sherman PW, Jarvis JUM, Alexander RD, eds. Princeton: Princeton University Press 66-96.

Judd TM, Sherman PW. 1996. Naked mole-rats recruit colony mates to food sources. Anim Behav 52: 957-969.

Katsumata M, Yamaguchi T, Ishida A, Ashihara A. 2017. Changes in muscle fiber type and expression of mRNA of myosin heavy chain isoforms in porcine muscle during pre- and postnatal development. Anim Sci J 88:364-371.

Kim EB, Fang X, Fushan AA, Huang Z, Lobanov AV, Han L, Marino SM, Sun X, Turanov AA, Yang P, Yim SH, Zhao X, Kasaikina MV, Stoletzki N, Peng C, Polak P, Xiong Z, Kiezun A, Zhu Y, Chen Y, Kryukov GV, Zhang Q, Peshkin L, Yang L, Bronson RT, Buffenstein R, Wang B, Han C, Li Q, Chen L, Zhao W, Sunyaev SR, Park TJ, Zhang G, Wang J, Gladyshev VN. 2011. Genome sequencing reveals insights into physiology and longevity of the naked mole-rat. Nature 479:223-7.

Kishida T. 2008. "Pattern of the divergence of olfactory receptor genes during tetrapod evolution." PLoS One 3(6): e2385.

Kruska DCT, and Steffen K. 2008. Encephalization of Bathyergidae and comparison of brain structure volumes between the Zambian mole-rat Fukomys anselli and the giant mole-rat Fukomys mechowii. Mammalian Biology-Zeitschrift für Säugetierkunde 74: 298-307.

Lacey EA, Alexander RD, Braude SH, Sherman PW, Jarvis JUM. 1991. An ethogram for the naked mole-rat: nonvocal behaviors. In The Biology of the Naked Mole Rat. Sherman PW, Jarvis JUM, Alexander RD, eds. Princeton: Princeton University Press, 209-242.

Lancet D, Ben-Arie N. 1993. "Olfactory receptors." *Current Biology* 3:668-674.

Larson J, Park TJ. 2009. Extreme hypoxia tolerance of naked mole-rat brain. Neuroreport 20:1634-1637.

Larson J, Drew KL, Folkow LP, Milton SL, Park TJ. 2014. No oxygen? No problem! Intrinsic brain tolerance to hypoxia in vertebrates. J Exp Biol 217:1024-39.

Laurie, DJ, Bartke, I, Schoepfer, R, Naujoks, K, Seeburg, PH. 1997. Regional, developmental and interspecies expression of the four NMDAR2 subunits, examined using monoclonal antibodies. Brain Res. Mol. Brain Res 51:23-32.

LaVinka PC, Brand A, Landau VJ, Wirtshafter D, Park TJ. 2009. Extreme tolerance to ammonia fumes in African naked mole-rats: animals that naturally lack neuropeptides from trigeminal chemosensory nerve fibers. J Comp Physiol A Neuroethol Sens Neural Behav Physiol 195:419-27.

LaVinka PC, Park TJ. 2012. Blunted behavioral and C Fos responses to acidic fumes in the African naked mole-rat. PLoS ONE 7(9):e45060.

Lee KS, Frank S, Vanderklish P, Arai A, Lynch G. 1991. Inhibition of proteolysis protects hippocampal neurons from ischemia. Proc Natl Acad Sci US. 88:7233-7237.

Liang S, Mele J, Wu Y, Buffenstein R, Hornsby PJ. 2010. Resistance to experimental tumorigenesis in cells of a long-lived mammal, the naked mole-rat (Heterocephalus glaber) Aging Cell. 9:626–635.

Liu Z, Wang W, Zhang TZ, Li GH, He K, Huang JF, Jiang XL, Murphy RW, Shi P. 2014. Repeated functional convergent effects of NaV1.7 on acid insensitivity in hibernating mammals. Proc Biol Sci 281(1776): 20132950.

Margulis SW, Saltzman W, Abbott DH. 1995. Behavioral and hormonal changes in female naked mole-rats (Heterocephalus glaber) following removal of the breeding female from a colony. Horm Behav 29:227-247.

Mason M J, Cornwall HL, Smith, ESJ. 2016. Ear structures of the naked mole-rat, Heterocephalus glaber, and its relatives (Rodentia: Bathyergidae). PloS ONE 11:e0167079

Mason MJ, Narins PM. 2010. Seismic sensitivity and communication in subterranean mammals In: O'Connell-Rodwell CE, editor. The Use of Vibrations in Communication: Properties, Mechanisms and Function across Taxa. Kerala: Kerala: Transworld Research Network 121-139.

Meneely G. 1974. The capillary factor in myocardial infarction. Am J Cardiol 34:581-587.

Meredith M, O'Connell RJ. 1979. Efferent control of stimulus access to the hamster vomeronasal organ. J Physiol 286:301-316.

Němec P, Cveková P, Benada O, Wielkopolska E, Olkowicz S, Turlejski K, Burda H, Bennett NC, Peichl L. 2008. The visual system in subterranean African mole-rats (Rodentia, Bathyergidae): retina, subcortical visual nuclei and primary visual cortex. Brain Res Bull 75:356-364.

Niimura, Y, Nei, M. 2006. Evolutionary dynamics of olfactory and other chemosensory receptor genes in vertebrates. J Hum Genet 51:505-517.

Omerbašić D, Smith ES, Moroni M, Homfeld J, Eigenbrod O, Bennett NC, Reznick J, Faulkes CG, Selbach M, Lewin GR. 2016. Hypofunctional TrkA accounts for the absence of pain sensitization in the African naked mole-rat. Cell Rep 17:748-758.

Oosthuizen MK, Bennett NC, Cooper HM. 2010. Photic induction of fos in the suprachiasmatic nucleus of Africa mole-rats: Responses to increasing irradiance. Chronobiol Int 27:1532-45.

O'Riain, MJ, Jarvis JUM. 1997. Colony member recognition and xenophobia in the naked mole-rat. Animal Behaviour 53:487-498.

Orr ME, Garbarino VR, Salinas A, Buffenstein R. 2016. Extended postnatal brain development in the longest-lived rodent: Prolonged maintenance of neotenous traits in the naked mole-rat brain. Front Neurosci 10:504.

Pamenter ME, Nguyen J, Carr JA, Powell FL. 2014. The effect of combined glutamate receptor blockade in the NTS on the hypoxic ventilatory response in awake rats differs from the effect of individual glutamate receptor blockade. Physiol Rep 2(8).

Pan J, Park TJ, Cutz E, Yeger H. 2014. Immunohistochemical characterization of the chemosensory pulmonary neuroepithelial bodies in the naked mole-rat reveals a unique adaptive phenotype. PLoS One 9(11):e112623.

Park TJ, Catania KC, Samaan D, and Comer CM. 2007. Adaptive neural organization of naked mole-rat somatosensation (and those similarly challenged). In Subterranean Rodents - News from Underground, S Begall, H Burda, CE Schleich (eds):175-93.

Park TJ, Reznick J, Peterson BL, Blass G, Omerbašić D, Bennett NC, Kuich PHJL, Zasada C, Browe BM, Hamann W, Applegate DT, Radke MH, Kosten T, Lutermann H, Gavaghan V, Eigenbrod O, Bégay V, Amoroso VG, Govind V, Minshall RD, Smith ESJ, Larson J, Gotthardt M, Kempa S, Lewin GR. 2017. Fructose-driven glycolysis supports anoxia resistance in the naked mole-rat. Science 356(6335):307-311.

Park TJ, Comer C, Carol A, Lu Y, Hong HS, Rice FL. 2003. Somatosensory organization and behavior in naked mole-rats: II. Peripheral structures, innervation, and selective lack of neuropeptides associated with thermoregulation and pain. J Comp Neurol 465:104-120.

Park TJ, Lu Y, Jüttner R, Smith ES, Hu J, Brand A, Wetzel C, Milenkovic N, Erdmann B, Heppenstall PA, Laurito CE, Wilson SP, Lewin GR. 2008. Selective inflammatory pain insensitivity in the African naked mole-rat (Heterocephalus glaber). PLoS Biol 6(1): e13.

Penz OK, Fuzik J, Kurek AB, Romanov R, Larson J, Park TJ, Harkany T, Keimpema E. 2015. Protracted brain development in a rodent model of extreme longevity. Sci Rep 5:11592.

Peterson BL, Larson, J, Buffenstein, R, Park, TJ, Fall, CP. 2012. Blunted neuronal calcium response to hypoxia in naked mole-rat hippocampus. PLoS One 7(2):e31568.

Peterson BL, Park TJ, Larson J. 2012. Adult naked mole-rat brain retains the NMDA receptor subunit GluN2D associated with hypoxia tolerance in neonatal mammals. Neurosci Lett 506:342-345.

Pickford M, Senut B, Morales J, Mein P, and Sanchez IM. 2008. Mammalia from the Lutetian of Namibia. Memoir of the Geological Survey of Namibia 20:465-514

Pilleri G. 1960. "Über das Zentralnervensystem von Heterocephalus glaber (Rodentia, Bathyergidae)." Acta Zoologica 41:101-111.

Pirlot P.1990. Brains of mole rats from Africa and North America. Prog Clin Biol Res 335:295-315.

Quay WB. 1981. Pineal atrophy and other neuroendocrine and circumventricular features of the naked mole-rat, heterocephalus glaber (Rüppell), a fossorial, equatorial rodent. J Neural Transm 52:107-115.

Russell WR. 1964. Some reactions of the nervous system to trauma. Br Med J 2:403-407.

Seki F, Hikishima K, Nambu S, Okanoya K, Okano HJ, Sasaki E, Okano H. 2013. Multidimensional MRI-CT atlas of the naked mole-rat brain (Heterocephalus glaber). Front Neuroanat 7:45.

Smith ES, Omerbašić D, Lechner SG, Anirudhan G, Lapatsina L, Lewin GR. 2011. The molecular basis of acid insensitivity in the African naked mole-rat. Science 334(6062):1557-1560.

Smith TD, Bhatnagar KP, Dennis JC, Morrison EE, Park TJ. 2007. Growth-deficient vomeronasal organs in the naked mole-rat (Heterocephalus glaber). Brain Res 1132:78-83.

Stathopoulos S, Bishop JM, O'Ryan, C. 2014. Genetic signatures for enhanced olfaction in the African mole-rats. PloS One 9(4):e93336.

Tian X, Azpurua J, Hine C, Vaidya A, Myakishev-Rempel M, Ablaeva J, Mao Z, Nevo E, Gorbunova V, Seluanov A. 2013. High-molecular-mass hyaluronan mediates the cancer resistance of the naked mole rat. Nature 499(7458):346-9.

Tirindelli R, Michele D, Pifferi S, Menini A. 2009. From pheromones to behavior. Physiol Rev 89:921-956.

Weiler E, McCulloch MA, Farbman AI. 1999. Proliferation in the vomeronasal organ of the rat during postnatal development. Eur J Neurosci 11:700-711.

Wilson KCP, Raisman G. 1980. Age-related changes in the neurosensory epithelium of the mouse vomeronasal organ: extended period of post-natal growth in size and evidence for rapid cell turnover in the adult. Brain Res 185:103-113.

Xiao J, Levitt JB, Buffenstein R. 2006. The use of a novel and simple method of revealing neural fibers to show the regression of the lateral geniculate nucleus in the naked mole-rat (Heterocephalus glaber). Brain Res 1077:81-89.

Figure Legends

Figure 1. A naked mole-rat in a university vivarium. Photo by Thomas Park and UIC Photo.

Figure 2. Somatic vibrissae and the tactile orienting response of naked mole-rats. **A.** Scanning electron micrographs of somatic vibrissa compared with facial vibrissae. **B.** The typical distribution of somatic vibrissae. The dashed lines indicate five zones arbitrarily used to distinguish the rostro-caudal locus of vibrissae stimulated during behavioral trials. **C.** Two examples of orientation responses when a vibrissa was deflected. The gray form shows the animal's position just before stimulation. The red outline shows animal's maximal turning position. The black lines indicate the body and head axes every 4 frames of the video. The small blue arrowhead shows the location of stimulation. **D.** Topography of orienting responses following stimulation of hairs along the rostro-caudal axis. From Crish et al., 2003a.

Figure 3. The vomeronasal organ (VNO) of the naked mole-rat shows no post-natal growth. **A-D.** The vomeronasal organs of two-week-old (A,C) and adult (B,D) naked mole-rats, illustrating that the vomeronasal neuroepithelium (*) is actually smaller in cross-sectional area in adults compared to infant pups. A and B are prepared with Gomori trichrome stain; C and D are prepared with Growth Associated Protein-43 (Gap43) which reveals growing axons. Although the neuroepithellium is approximately equal in average volume comparing infants to adults, it is neurogenic throughout life, as revealed by Gap43 immunohistochemistry (see Smith et al., this

issue). Scale bars: A, B, 50 micrometers; C, D, 20 micrometers. **E,F.** vnne volume as a function of age in naked mole-rats and laboratory rats. From Smith et al., 2007.

Figure 4. Naked mole-rats brain shows extreme intrinsic tolerance to hypoxia and anoxia in the hippocampal brain slice preparation. **A.** The graph shows field excitatory postsynaptic potential (fEPSP) responses of a mouse (open circles) and a naked mole-rat (filled circles), normalized to 100% of baseline amplitude for each animal. The bar labeled "15% O_2" indicates a 30-minute period when the O_2 concentration was reduced from 95% to 15%. The traces are examples taken from before and during exposure to 15% O_2, mouse on the left, naked mole-rat on the right. NMR = naked mole-rat. **B.** Same as A except with 10% O_2. **C.** Summary data showing average maximum decrease from hypoxia at each concentration of O_2 tested. **D.** Summary data showing percentage of slices that recovered from each concentration of O_2 tested. **E**. Response to 0% O_2, the black bar indicates the duration required for the naked mole-rat slice to reach anoxic depolarization (AD), associated with loss of synaptic function. F. The bars show average time to AD, measured at two temperatures. From Larson and Park, 2009.

Figure 5. Intact naked mole-rats show extreme resistance to hypoxia (5% O_2) and anoxia (0% O_2). **A**. Mice and naked mole-rats were exposed to 5% O_2. Mice ceased breathing attempts after about 12 minutes and did not recover. **B**. Exposure to 0% O_2. **C**. Percent of mice and naked mole-rats that recover from different durations of anoxia. **D**. Respiration rate and **E** heart rate in naked mole-rats during 18 minutes of anoxia followed by normoxia (black curve = mice). Error bars are standard errors. From Park et al., 2017.

Figure 6. Effect of switching glucose to fructose on functionality of hippocampal brain slices and isolated hearts. **A**. Schematic of the slice preparation and example fEPSP traces (left). The graph shows average fEPSPs (as percent of control) before, during, and after bath glucose was switched to fructose for 1 hour. **B**. Left ventricular developed pressure (LVDP), a typical measure of cardiac function, measured from isolated, beating hearts from naked mole-rats and mice. The traces show LVDP (as percent of control) before, during, and after two successive switches from bath glucose to fructose. From Park et al, 2017.

Figure 7. Responses of mice and naked mole-rats to high concentrations of CO_2. **A** and **B.** In an avoidance test, mice (A) spent more time in room air (Air) than in 2.5%, 5%, or 10% CO_2. Naked mole-rats (B) only showed avoidance to 10% CO_2. **C.** Lung wet-to-dry weight ratios (a measure of pulmonary edema) as a function of CO_2 concentration. Animals were exposed for 15 minutes before lungs were weighed. From Park et al., 2017.

Figure 8. Responses of mice and naked mole-rats in a variety of pain models. **A.** The bars show response latency to acute mechanical stimulation (pinch) and acute thermal stimulation. **B.** Time spent licking the injection site for capsaicin solution or acidic solution. **C.** Thresholds for paw withdrawal before and after inflammation with complete Freund's adjuvant (CFA). **D-F.** Latencies for foot withdrawal to heat before and after inflammation from capsaicin (Cap) or nerve growth factor (NGF). **G.** Pain scores for mice (left) and naked mole-rats (right) after foot injection of 1% formalin. From Park et al., 2008.

Figure 9. Rescue of capsaicin-induced sensitization to heat one week after infection of one paw with transgenic herpes virus carrying the preprotachykinin (PPT) gene for Substance P. The paw treated with the virus (PPT Virus) shows sensitization from capsaicin (shorter latency to withdrawal from heat) compared to the paw not treated with the virus (No Virus). From Park et al., 2008.