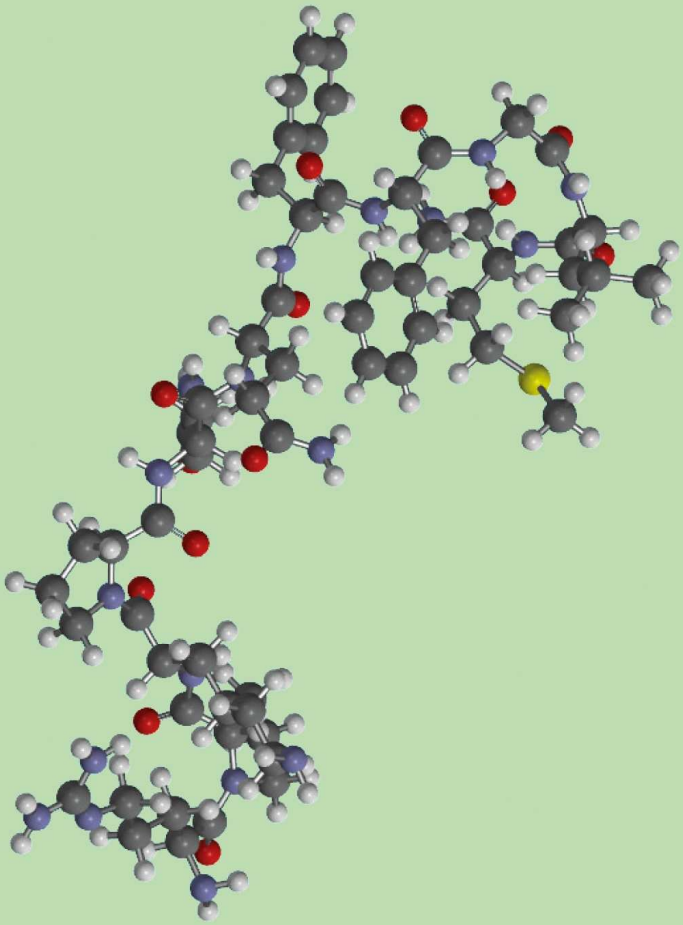
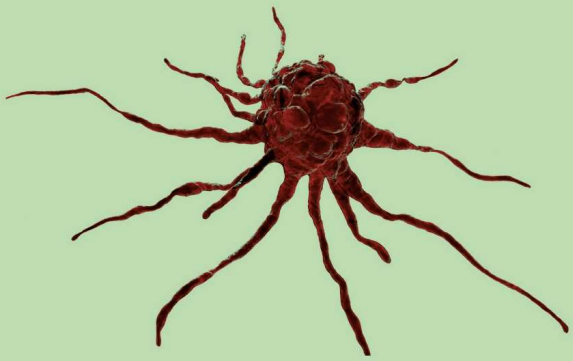
Substance P

From Pain to Cancer





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Molecular Mediators in Health and Disease: How Cells Communicate

CHAPTER

Life without substance P: The naked mole rat

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1 Introduction

The African naked mole rat (*Heterocephalus glaber)* is a small, eusocial rodent that lives in large colonies consisting of up to 295 individuals [1,2]. Their skin is pink and translucent, and naked mole rats have a distinct set of incisors that protrude externally from the mouth so that they can close their lips behind their teeth while using the teeth to dig tunnels, toilets, and nest chambers [3]. They construct and inhabit complex underground tunnel systems in the Horn of Africa where they are protected from climate extremes and predators on the surface, but still face limited resources (sparsely distributed food), and a biologically challenging environment where there is a depletion of oxygen and an accumulation of carbon dioxide from many respirating individuals living in an unventilated space [4]. This is particularly an issue in the communal nest chambers where animals gather to huddle and sleep.

Data from Zions et al. [5] show that the nest chambers in colonies of captive naked mole rats have significantly, and substantially higher concentrations of CO_2 compared to other compartments in the housing system (Fig. 1A). They also showed that on average, colony members spent more than 70% of their time in the nest chamber, exposed to elevated CO_2. Fig. 1B is a photograph showing many members of a captive colony at the University of Illinois Chicago huddling together in a nest chamber. Fig. 1C is a photograph of an individual naked mole rat being held in a researcher's hand so that the reader can gauge the size of these animals.

Naked mole rats have a multitude of biological adaptations that make them specialized for life in humid, congested, poorly ventilated burrows. Subsequently, this species is a fascinating and important nontraditional model for biomedical research.

*Aishi Zhao and Jiwon Lee made equal contributions and are the first authors of this chapter.

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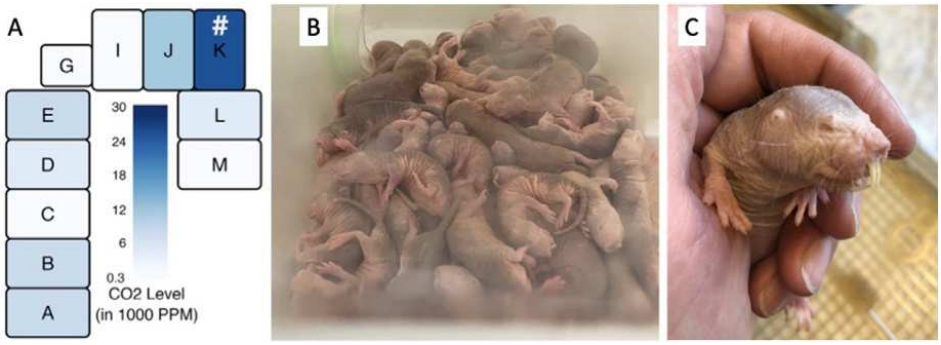

FIG. 1

In the laboratory, naked mole rats establish a nest chamber where they huddle and sleep. (A) Zions et al. [5] recorded CO_2 levels and time spent in the nest chamber averaged over 26 days and across two colonies. The schematic shows CO_2 levels in a housing system made up of 11 chambers. The nest chamber (chosen by the animals) is indicated by the # symbol. (B) This photograph shows typical huddling behavior in a nest chamber for a colony of naked mole rats at the University of Illinois Chicago. Photo by Thomas Park. (C) This photograph shows the average size of an adult naked mole rat. Photo by Thomas Park.

Studies have focused on topics such as tolerance to hypoxia and hypercapnia, extreme longevity, resistance to cancer, and insensitivity to chemical pain [6–11].

One remarkable feature that naked mole rats display is the lack of Substance P from their peripheral nerves [9,12]. Substance P is associated with pain from a variety of irritants such as carbon dioxide (CO_2), acid, capsaicin, and ammonia, as well as itch-like pruritogen, like histamines. Lack of Substance P is presumably an adaptation to reduce the negative effects of living in a high CO_2 atmosphere, which would cause a burning sensation in the nasal cavity and around the eyes, as well as acidosis in the lungs that causes pulmonary edema. This chapter reviews how this feature affects their physiology and behavior. For example, naked mole rats show a blunted response to inflammatory pain, complete insensitivity to irritants such as capsaicin, ammonia, and acid, and they do not show a scratching response to histamine.

1.1 Pain and itch

Pain is defined as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" according to the International Association for the Study of Pain [13]. In a basic behavioral model of pain, an organism in pain is motivated to withdraw from or act to reduce the pain sensation. There are many different types of pain and different ways to classify them. Acute pain has a sudden onset, immediately after an injury, and often calls for quick withdrawal from the stimulus; chronic pain continues even after the typical time period for healing [14].

Nociceptive pain, caused by damage to body tissue, is a response to intense stimuli, such as extreme heat, cold, pressure, or noxious chemicals [15,16]. For example, spraining an ankle while running or touching a hot bowl would cause nociceptive pain. Inflammatory pain is a type of nociceptive pain, in a reaction to foreign substances—such as bacterial infections—or injuries, and it involves the release of cytokines by immune cells [15]. Neuropathic pain is caused by damage to nerve cells, typically with poor localization, and is described as tingling, sharp, prickling, burning, or shooting pain [14]. Sensory dysfunctions such as allodynia, hyper- and hypoalgesia, paresthesia, and dysesthesia are often associated with neuropathic pain [14].

Pain is detected by sensory receptors for noxious stimuli on peripheral sensory neurons called nociceptors. Nociceptors are composed of two different types of nerve fibers—myelinated A-δ fibers and unmyelinated C fibers [17]. A-δ fibers respond to mechanical pain or hot temperature pain. They release glutamate at their synapse in the spinal cord, and when stimulated, the perception of pain is relatively short and well localized. C fibers are polymodal, responding to mechanical pain, cold pain, hot pain (<50°C), inflammatory pain, and chemical pain. C fibers release glutamate as well as Substance P (and the other neuropeptides, neurokinin A (NKA) and calcitonin gene-related peptide (CGRP)) at their synapse in the spinal cord, and when stimulated, the perception of pain is relatively long-lasting and relatively diffusely localized. C fibers also release neuropeptides near the site of stimulation.

In addition to carrying information about pain, C-fibers additionally carry information related to itch [18]. Itch is an uncomfortable sensation that triggers a strong desire for scratching behavior and is associated with common inflammatory skin disorders [19]. Various pruritogens, which are defined as stimuli that interact with sensory neurons to cause itch sensations, have been identified in previous studies [20]. The most well-known pruritogen, histamine, activates C-fibers, which is thought to trigger itch [19,21]. The transient receptor potential vanilloid 1 (TRPV1) receptor, a capsaicin-activated ion channel, facilitates this relationship between histamine and C-fibers, as TRPV1 knockout mice were found to exhibit significantly less histamine-induced scratching behavior [22].

Rodents typically have both myelinated and unmyelinated fibers throughout their skin, and the same is true for naked mole rats [9]. Fig. 2A highlights that laboratory mice and naked mole rats are similar in overall size and foot size. Fig. 2B and C show electron microscope cross sections through the saphenous nerve, revealing myelinated and unmyelinated fibers in both species. Interestingly, Fig. 2D shows that naked mole rats have a smaller proportion of unmyelinated fibers to myelinated fibers compared to mice and other mammals [23].

Fig. 2E and F shows that within unmyelinated C fibers, mice and naked mole rats have similar proportions of fibers containing isolectin B4 ($IB4^+$) and fibers not containing isolectin B4 ($IB4^-$). $IB4^-$ fibers are normally associated with peptidergic nociceptors, those containing Substance P, while $IB4^+$ fibers are normally associated with nonpeptidergic nociceptors [24]. Even though naked mole rats have two distinct populations of C fibers, $IB4^-$ and $IB4^+$, immunolabeling revealed that the small diameter unmyelinated skin fibers of naked mole rats do not express substance P (or CGRP) [9,12].

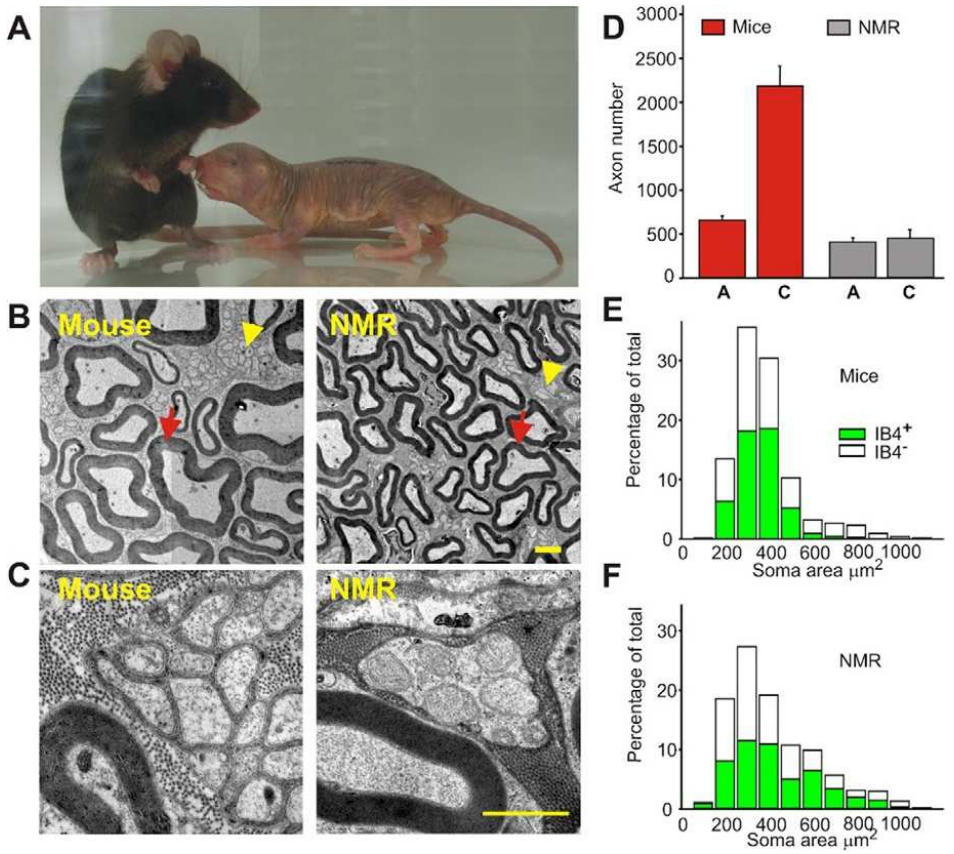

FIG. 2

Myelinated and unmyelinated fibers in the saphenous nerve of laboratory mice and naked mole rats. (A) The photograph shows that the overall body size and the size of the feet are similar for mice and naked mole rats. (B and C) These electron micrographs show myelinated axons (*red arrows*) and unmyelinated axons within Remak bundles (*yellow arrows*) in saphenous nerves from mice and naked mole rats. Scale bars are 2.0 μm (C is at a higher magnification than B). (D) The bar graph shows a quantification of myelinated axons (panel "A") and unmyelinated axons (panel "C"). (E and F) The bar graphs show a quantification of isolectin B4 negative ($IB4^-$) (peptidergic) and IB4 positive ($IB4^+$) (nonpeptidergic) C fibers for mice and naked mole rats.

This figure is from Park, T. J., Lu, Y., Jüttner, R., Smith, E.S., Hu, J., Brand, A., Wetzel, C., Milenkovic, N., Erdmann, B., Heppenstall, P. A., Laurito, C.E., Wilson, S.P., Lewin, G. R. Selective inflammatory pain insensitivity in the African naked mole-rat (Heterocephalus glaber). PLoS Biol 2008;6(1):e13. https://doi.org/10.1371/journal.pbio.0060013.

2 Reduced or absent sensitivity to elevated CO_2 and fumes from other irritants

As mentioned earlier, naked mole rats tend to spend much of their time in the crowded colony nest chamber, which has elevated concentrations of CO_2 [5]. Elevated concentrations of CO_2 can cause tissue acidosis along with associated behavioral and physiological responses. Park et al. [6] found that naked mole rats were more tolerant to hypercapnic environments in a study comparing mice and naked mole rats in avoidance tests. The experimental setup included an oblong rectangular testing arena where CO_2 was infused into one end and room air was infused into the other end. The researchers measured the amount of time each animal spent within 10 cm of the ends of the arena. Three hypercapnic conditions were tested: 2.5%, 5%, and 10% CO_2. Fig. 3A shows that the mice spent much more time near the room air end of the arena than the CO_2 end for all three concentrations of CO_2 (i.e., they avoided each concentration of CO_2). On the other hand, the naked mole rats only avoided 10% CO_2 (Fig. 3B).

A related study showed that naked-mole rats do not avoid fumes from 10% ammonia (household cleaning ammonia) or 20% acetic acid (Fig. 4) [25]. Both irritants activate C fiber nociceptors in other mammals, and as seen in the figure, laboratory rats, mice, and Damaraland mole rats avoided these irritants at a significant rate.

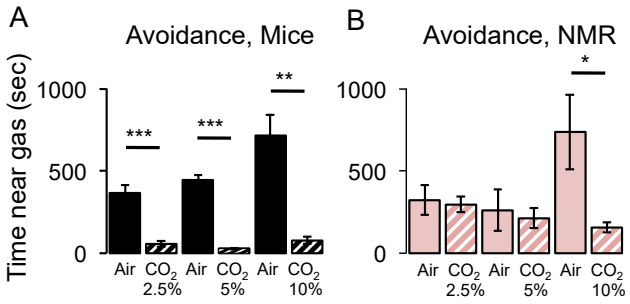

FIG. 3

Responses to avoidance tests of naked mole rats and mice in elevated CO_2 environments. (A) Results from mice indicate that they avoid all three concentrations of CO_2. (B) Results from naked mole rats indicate that they only avoid the highest concentration tested. Data shown as mean +/− S.E.M. $*P<0.05$, $**P<0.01$, $***P<0.001$.

This figure is from Park, T. J., Reznick, J., Peterson, B. L., Blass, G., Omerbašić, D., Bennett, N. C., Kuich, P. H. J. L., Zasada, C., Browe, B. M., Hamann, W., Applegate, D. T., Radke, M. H., Kosten T, Lutermann, H., Gavaghan, V., Eigenbrod, O., Bégay, V., Amoroso, V. G., Govind, V., Minshall, R. D., Smith, E. SJ., Larson, J., Gotthardt, M., Kempa, S., Lewin, G. R. Fructose-driven glycolysis supports anoxia resistance in the naked mole-rat. Science 2017;356:307–311.

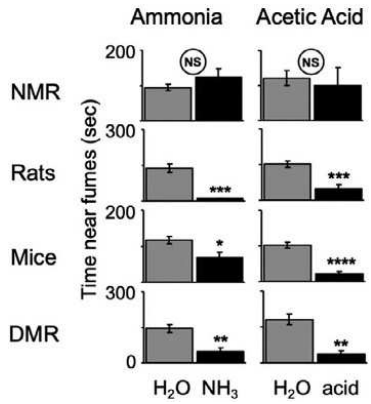

FIG. 4

Naked mole rats do not avoid fumes from ammonia or acetic acid, irritants that activate C fibers. The experimental set up was similar to that described for Fig. 3 except that the fumes derived from sponges saturated with ammonia versus water or acetic acid versus water. Naked mole rats (NMR) did not avoid areas with irritant sponges, whereas rats, mice, and Damaraland mole rats (DMR) showed significant avoidance. $*P < 0.05$, $**P < 0.01$, $***P < 0.001$, $****P < 0.0001$.

This figure is from LaVinka, P. C., Park, T. J. Blunted behavioral and C Fos responses to acidic fumes in the African naked mole-rat. PLoS One 2012;7(9):e45060. https://doi.org/10.1371/journal.pone.0045060.

3 Lack of pulmonary edema from hypercapnia

Breathing elevated concentrations of CO_2 can induce pulmonary edema, a life-threatening condition where there is abnormal buildup of fluid in the lungs. CO_2 affects alveolar permeability and reabsorption properties of the lung, then acidifies lung tissue that activates acid-sensitive sensory nerves causing neurogenic inflammation and edema [26]. Naked mole rats do not show pulmonary edema even at high concentrations of CO_2 (50%) compared to mice that start showing significant edema at 15% CO_2 [6]. Fig. 5 shows a percent increase in lung wet-to-dry ratios for mice and naked mole rats after breathing various elevated concentrations of CO_2 for 15 min.

4 Pain responses

4.1 Lack of cutaneous pain from capsaicin and rescue with extrinsic substance P

Capsaicin, the spicy ingredient in chili peppers, activates the TRPV1 ion channel, which is predominantly expressed by unmyelinated C-fibers that express Substance P (i.e., peptidergic C-fibers) [27]. An obvious question is, how do naked mole rats, a species that lacks Substance P from its C fibers, respond to capsaicin?

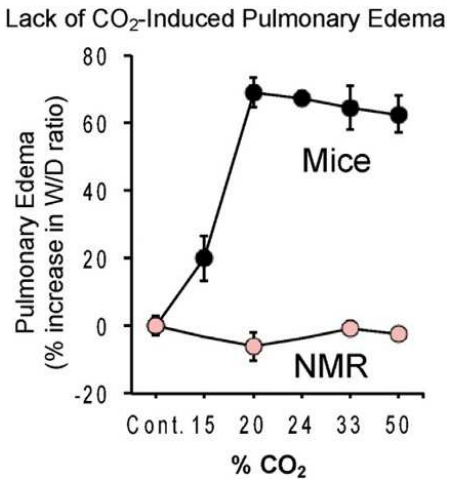

FIG. 5

Lack of CO_2-induced pulmonary edema in naked mole rats. Laboratory mice and naked mole rats were exposed to a specified concentration of CO_2 for 15 min before removing the lungs and determining their weight. The lungs were then dried overnight and weighed again to determine their wet-to-dry ratio as a measure of pulmonary edema. The curves represent the percent change in lung wet-to-dry ratio as a function of the CO_2 concentration in the atmosphere.

This figure is from Park, T. J., Reznick, J., Peterson, B. L., Blass, G., Omerbašić, D., Bennett, N. C., Kuich, P. H. J. L., Zasada, C., Browe, B. M., Hamann, W., Applegate, D. T., Radke, M. H., Kosten T, Lutermann, H., Gavaghan, V., Eigenbrod, O., Bégay, V., Amoroso, V. G., Govind, V., Minshall, R. D., Smith, E. SJ., Larson, J., Gotthardt, M., Kempa, S., Lewin, G. R. Fructose-driven glycolysis supports anoxia resistance in the naked mole-rat. Science 2017;356: 307–311.

The answer is intriguing. Behaviorally, they are completely insensitive to the injection of capsaicin solution into the skin of the foot. However, physiologically, their C fibers respond to capsaicin similarly to the C fibers of other mammals [9]. Fig. 6A shows results from the capsaicin test on laboratory mice and naked mole rats. Mice show a robust licking response. In contrast, naked mole rats show virtually no behavioral response. Fig. 6B shows physiological results from testing naked mole rat C fibers in the Skin Nerve Preparation. Remarkably, naked mole rat C fibers respond to capsaicin.

So, naked mole rat C fibers respond to capsaicin, but the animals do not show a behavioral response to capsaicin. Knowing that naked mole rat C fibers lack Substance P, Park et al. [9] hypothesized that introducing Substance P might rescue capsaicin-elicited pain behavior. To test this idea, they introduced Substance P in two different ways. In one cohort of naked mole rats, they infected one hind foot with a transgenic herpes virus expressing the preprotachykinin gene for Substance P (and neurokinin A) (Fig. 7A, top). One week later, the infected foot showed a robust sensitization to heat when capsaicin was applied topically (Fig. 7B). In a separate cohort of naked mole rats, they used intrathecal injection of Substance P (Fig. 7A, *bottom*).

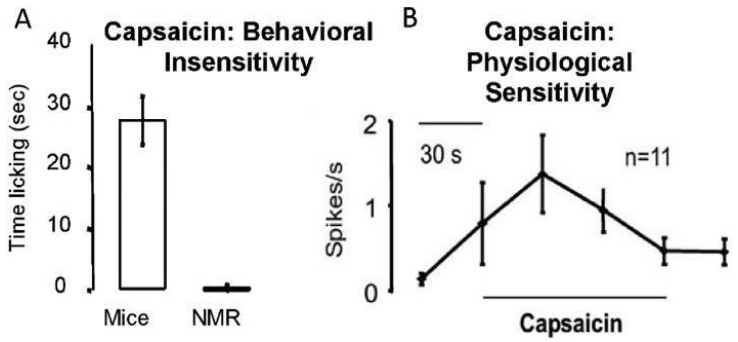

FIG. 6

Naked mole rats do not show pain behaviors to capsaicin injection, even though their C fibers respond physiologically to capsaicin. (A) Injecting one hind foot with capsaicin results in robust licking at the injection site for mice but not naked mole rats. (B) Despite behavioral insensitivity, naked mole rat C fibers show substantial responses to capsaicin in the Skin Nerve Preparation.

This figure is from Park, T. J., Lu, Y., Jüttner, R., Smith, E.S., Hu, J., Brand, A., Wetzel, C., Milenkovic, N., Erdmann, B., Heppenstall, P. A., Laurito, C.E., Wilson, S.P., Lewin, G. R. Selective inflammatory pain insensitivity in the African naked mole-rat (Heterocephalus glaber). PLoS Biol 2008;6(1):e13. https://doi.org/10.1371/journal.pbio.0060013.

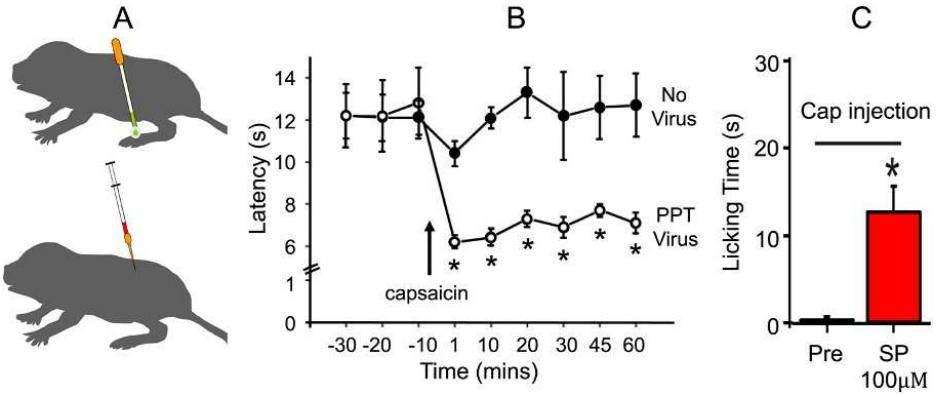

FIG. 7

Introduction of Substance P rescues pain behaviors from capsaicin. (A) Substance P was introduced in two different ways: via infection with a herpes virus expressing the preprotachykinin gene (PPT), and via intrathecal injection of Substance P. (B) One week after infection with the herpes virus (labeled "PPT Virus"), foot withdrawal latency to heat was sensitized for the infected foot (shorter latencies) in response to topical application of capsaicin. The noninfected foot (labeled "No Virus") did not show sensitization from the application of capsaicin. (C) Intrathecal injection of Substance P rescued pain behavior: licking the site of capsaicin injection.

This figure is from Park, T. J., Lu, Y., Jüttner, R., Smith, E.S., Hu, J., Brand, A., Wetzel, C., Milenkovic, N., Erdmann, B., Heppenstall, P. A., Laurito, C.E., Wilson, S.P., Lewin, G. R. Selective inflammatory pain insensitivity in the African naked mole-rat (Heterocephalus glaber). PLoS Biol 2008;6(1):e13. https://doi.org/10.1371/journal.pbio.0060013.

These naked mole rats showed pain behavior (licking) in response to foot injection of capsaicin solution (Fig. 7C). Hence, both techniques for introducing Substance P resulted in a rescue of pain behaviors for capsaicin.

4.2 Lack of cutaneous pain from acid but no rescue with extrinsic substance P

Acid is usually considered to be a painful stimulus, mediated by TRPV1 receptors as well as a host of other acid receptors such as acid-sensing ion channels (ASICs) and a variety of others [28]. However, naked mole rats are neither behaviorally (Fig. 8A), nor physiologically (Fig. 8B) sensitive to acid [9]. Furthermore, introducing Substance P via intrathecal injection does not rescue acid pain (Fig. 8C) as it did capsaicin pain.

The fact that introducing Substance P does not rescue acid pain, as it did capsaicin pain, suggests that an additional mechanism contributes to acid insensitivity. Smith et al. [29] discovered that naked mole rats have a mutated voltage-gated sodium channel 1.7 (Nav1.7) on C fibers that would normally convey excitation from acid. This leads to a blockade in acid-induced action potentials, resulting in insensitivity to acid. However, these C fibers would still be able to fire action potentials initiated by other noxious stimuli.

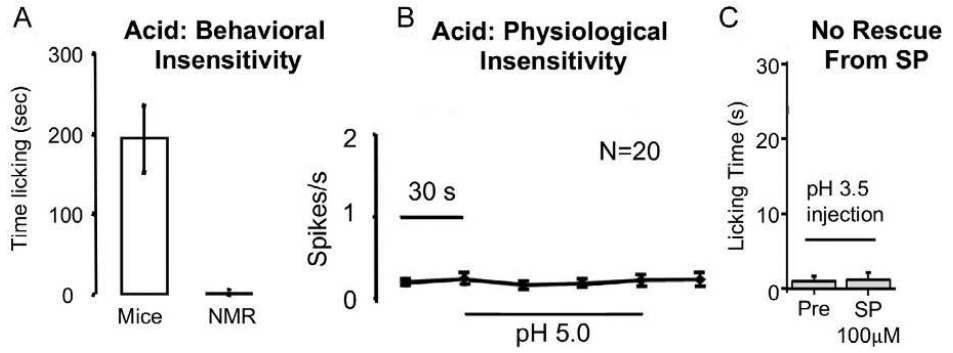

FIG. 8

Naked mole rats are insensitive to acid pain. (A) Injection of acidic saline into the skin of the foot induces robust licking in mice, but virtually no response from naked mole rats. (B) Naked mole rat C fibers do not respond to acid in the Skin Nerve Preparation. (C) Intrathecal injection of Substance P (SP) does not rescue acid pain.

This figure is from Park, T. J., Lu, Y., Jüttner, R., Smith, E.S., Hu, J., Brand, A., Wetzel, C., Milenkovic, N., Erdmann, B., Heppenstall, P. A., Laurito, C.E., Wilson, S.P., Lewin, G. R. Selective inflammatory pain insensitivity in the African naked mole-rat (Heterocephalus glaber). PLoS Biol 2008;6(1):e13. https://doi.org/10.1371/journal.pbio.0060013.

4.3 Reduced inflammatory pain in the formalin test and rescue with extrinsic substance P

The formalin test is a medium-term model of inflammatory pain that involves both peptidergic and nonpeptidergic pain fibers [30]. Park et al. [9] showed that naked mole rats have reduced pain behaviors in the formalin test compared to mice (Fig. 9A and B). In a following study, Browe et al. [31] showed that intrathecal injection of Substance P increased pain behaviors in naked mole rats (Fig. 9C). The authors also demonstrated that the nonpeptidergic C fiber pathway (IB4+) is functional in naked mole rats. This is possibly why naked mole rats show a response in the formalin test, albeit a reduced response (Fig. 9B), that increases when exogenous Substance P allows the peptidergic pathway (IB4-) to contribute to pain behaviors (Fig. 9C).

4.4 Normal pain behavior to acute mechanical and acute heat stimuli

Naked mole rats react normally (mouse-like) to acute mechanical stimuli (i.e., pinch) and acute thermal stimuli (i.e., heat). Fig. 10 shows the latency of foot withdrawal to tail pinch (Fig. 10A) and radiant heat (Fig. 10B) for mice and naked mole rats. There are no significant species differences.

5 Lack of itch from histamine and rescue with extrinsic substance P

In addition to pain sensing, Substance P is also involved in mediating the sense of itch [22,32]. Smith et al. [33] showed that naked mole rats, like mice, show a low rate of spontaneous scratching (Fig. 11A). However, unlike mice, naked mole rats show virtually no scratching behavior from intracutaneous injection of the strong pruritogen, histamine (Fig. 11B).

Smith et al. [33] went on to show that exogenous Substance P could rescue scratching behavior to histamine (Fig. 12). In that study, naked mole rats and mice were given an intrathecal injection of Substance P or saline followed by an intracutaneous injection of histamine or saline. Fig. 12A shows that naked mole rats only responded with substantial scratching for the treatment of intrathecal Substance P and intracutaneous histamine (*red bar*). Mice, on the other hand (Fig. 12B) also showed substantial scratching for the treatment of intrathecal saline (control) and intracutaneous histamine (*black bar*), as would be expected.

6 Discussion

Naked mole rats do not express Substance P in their C fibers, and they display behavioral and physiological characteristics that are consistent with a lack of Substance P. For example, they show virtually no pain behaviors to intracutaneous injection

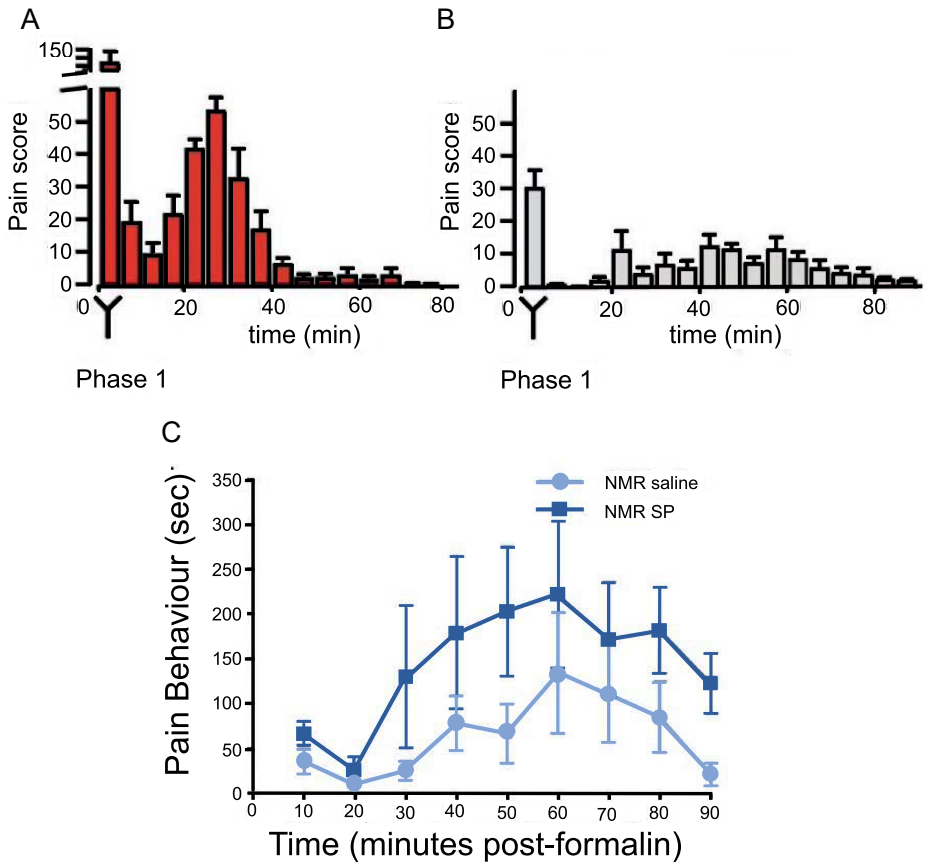

FIG. 9

Naked mole rats show a reduced response in the formal test that increases after intrathecal injection of Substance P. (A) The graph shows pain scores for mice in the formalin test. (B) The graph shows pain scores for mice in the formalin test. (C) Naked mole rats show an increase in pain behaviors after an intrathecal injection of Substance P compared to an intrathecal injection of saline. Note that data collection for A and B used a scoring system. A score of 3 was assigned for a foot lick, a 2 for a foot lifted off the ground, and a 1 for favoring the formalin-injected foot (limping). The data collection for C used a different scoring system, which measured cumulative time licking and lifting the formalin-injected foot.

Panel (A) and (B) are from Park, T. J., Lu, Y., Jüttner, R., Smith, E.S., Hu, J., Brand, A., Wetzel, C., Milenkovic, N., Erdmann, B., Heppenstall, P. A., Laurito, C.E., Wilson, S.P., Lewin, G. R. Selective inflammatory pain insensitivity in the African naked mole-rat (Heterocephalus glaber). PLoS Biol 2008;6(1):e13. https://doi.org/10.1371/journal.pbio.0060013. Panel (C) is from Browe, B. M., Olsen, A.R., Ramirez, C., Rickman, R. H., Smith, E. SJ., Park, T. J. The naked mole-rat has a functional purinergic pain pathway despite having a non-functional peptidergic pain pathway. Neurobiol. Pain 2020;8:100047. https://doi.org/10.1016/j.ynpai.2020.100047.

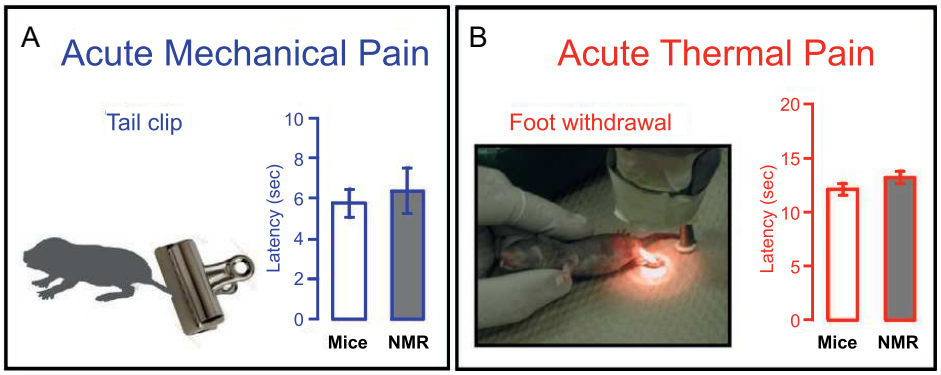

FIG. 10

Foot withdrawal in response to pinch and heat. (A) Naked mole rats and mice have the same withdrawal latency to 450g of pressure to the base of the tail from a tail clip. (B) Similarly, naked mole rats and mice have the same withdrawal latency to radiant heat on the hind paw delivered by a calibrated heat source.

*This data is from Park, T. J., Lu, Y., Jüttner, R., Smith, E.S., Hu, J., Brand, A., Wetzel, C., Milenkovic, N., Erdmann, B., Heppenstall, P. A., Laurito, C.E., Wilson, S.P., Lewin, G. R. Selective inflammatory pain insensitivity in the African naked mole-rat (*Heterocephalus glaber*). PLoS Biol 2008;6(1):e13. https:/doi.org/10.1371/journal.pbio.0060013.*

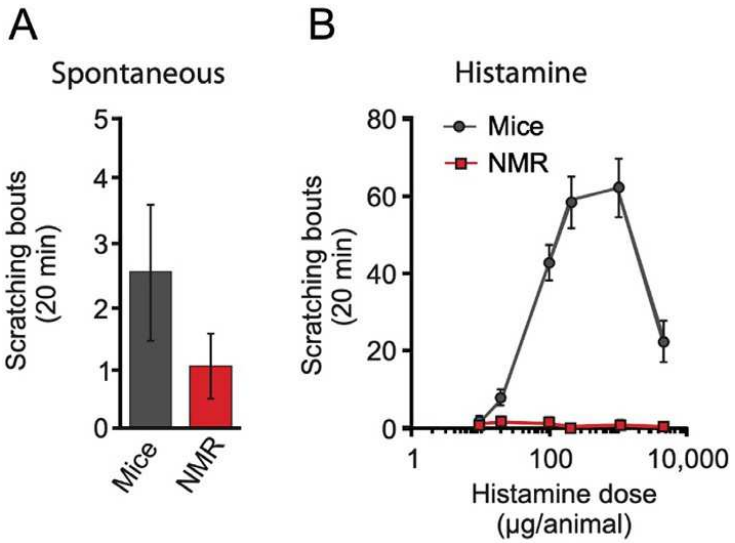

FIG. 11

Spontaneous and histamine-induced scratching. (A) Both mice and naked mole rats show a similarly low rate of spontaneous scratching. (B) The graph shows bouts of scratching from intracutaneous injection of histamine into the nape of the neck for various doses of histamine. Mice show robust scratching for a variety of doses while naked mole rats do not.

This data is from Smith, E St John, Blass, G. R., Lewin, G. R., Park, T. J. (2010). Absence of histamine-induced itch in the African naked mole-rat and "rescue" by substance P. Mol Pain 2010; 6(1): 29–29. https:/doi.org/10.1186/1744-8069-6-29.

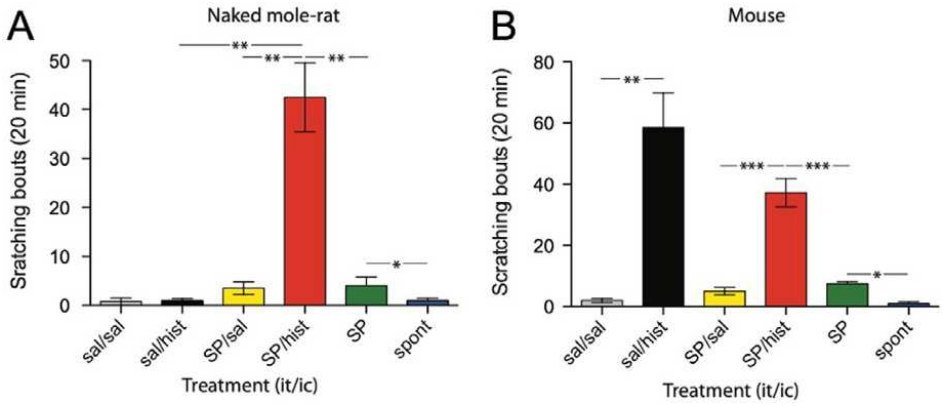

FIG. 12

Intrathecal injection of Substance P rescues histamine-induced scratching in naked mole rats. (A) The graph shows bouts of scratching for naked mole rats after various treatments. The only treatment that drove substantial scratching was an intrathecal (it) injection of Substance P followed by intracutaneous (ic) injection of histamine (*red bar*). (B) The results from mice show that histamine drove substantial scratching both with and without intrathecal injection of Substance P.

These data are from Smith, E St John, Blass, G. R., Lewin, G. R., Park, T. J. Absence of histamine-induced itch in the African naked mole-rat and "rescue" by substance P. Mol Pain, 2010; 6(1): 29–29. https:/doi.org/10.1186/1744-8069-6-29.

of capsaicin, and virtually no scratching behaviors to intracutaneous injection of histamine. However, introducing exogenous Substance P rescued both pain and scratching behaviors for these stimuli. These findings are intriguing because they imply that all of the machinery for these Substance P-related effects are viable in this species, including functional neurokinin 1 receptors and postsynaptic circuits.

Another intriguing aspect of naked mole rat biology involves acid insensitivity. Lack of Substance P alone would be expected to blunt acid pain. Yet, in addition to the lack of Substance P, naked mole rats have a mutation in voltage-gated sodium channel 1.7, which results in complete insensitivity to acid pain. Are these two phenomena redundant? At this time, we do not know.

It is worth noting that the lack of Substance P and the mutation in sodium channel 1.7 are only two adaptations among myriad putative adaptations that this species displays for surviving and thriving in their challenging environment. In addition to living in high concentrations of CO_2, which would cause tissue acidosis and pain, the atmosphere in naked mole rat burrows is likely low in O_2 [4]. Recall that naked mole rats are unusual among mammals because they combine a subterranean lifestyle with living in large colonies where many individuals are respirating, generating both high concentrations of CO_2 and low concentrations O_2 (hypoxia). These conditions become even more extreme in densely populated areas of their burrows, such as the nesting chamber. It is beyond the scope of this chapter to detail the various

adaptations that this species displays for tolerating a hypoxic environment. However, it is worth mentioning that they show intrinsic brain tolerance to hypoxia; reduced accumulation of intracellular calcium during hypoxia; the ability to conserve energy by going into a state of suspended animation during hypoxia; and the ability to use fructose instead of glucose to maintain anaerobic metabolism during hypoxia [6,34,35]. Naked mole rats are also unusual mammals because they are poikilothermic, taking on the temperature of their surroundings [36]. A great deal of information about naked mole rats, including the adaptations discussed earlier, as well as their unusual social structure, immune system, aging, cancer resistance, and husbandry, among other topics can be found in [37].

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