NATIONAL CENTER FOR CASE STUDY TEACHING IN SCIENCE

Not the NMR You Are Thinking of:
Mammalian Metabolism in Anoxic Conditions

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Introduction

From the title, perhaps you are already preparing yourselves for a journey through nuclear magnetic resonance (NMR), a tool commonly used in organic chemistry and structural investigation of small proteins. Not in this case; here, NMR is an acronym for a weird mammal, the naked mole-rat (*Heterocephalus glaber*). Naked mole-rats are furless, pink, blind critters that have evolved to live in subterranean caves and tunnels. "Superpowers" of naked mole-rats have escaped our discovery for years. In this case study, we will explore the amazing life of naked mole-rats while reviewing the basics of carbohydrate metabolism.

Why am I doing this exercise?

This case study is designed to help you:

- Understand glycolytic metabolism.
- Differentiate the allosteric regulation of glycolysis.
- Practice reading a scientific paper.
- Analyze scientific data.
- Make evidence-based conclusions.
- Apply theories and knowledge to solve real-life issues.

Part I – Ecology of the Naked Mole-Rat

Watch the following two videos and then answer the questions on the next page.

- *The Naked Mole-Rat:* <https://youtu.be/wyx6jcp9zfQ>

  This interview with Field Museum curator Dr. Bruce Patterson explains why naked mole-rats have recently been promoted into their own taxonomic family. Running time: 10:03 min. Produced by The Brain Scoop, 2015.

- *Why Observing Naked Mole-Rats is Never an Easy Task:* <https://youtu.be/Mfh6iLZS6Ew>

  This overview of naked mole-rat behavior and ecology adopts the view that "If you don't understand what an animal is doing in its natural habitat, then you don't truly understand any of the other things." Running time: 2:50 min. Produced by Smithsonian Channel, 2020.

Questions

1. Why has the naked mole-rat escaped our study for a very long time?

2. Naked mole-rats are said to be eusocial, which is a term often used to describe insects like ants and bees. In what ways are naked mole-rats like ants and bees?

3. How is the social behavoir of naked mole-rats similar to that of humans? How is it different?

4. Naked mole-rats are poikilothermic animals, which means that their internal temperature varies with their surroundings. What is an advantage and a disadvantage of this strategy compared to animals that keep their body temperature constant?

5. According to the assigned videos, how did naked mole-rats evolve to be poikilothermic?

6. Why are scientists interested in studying naked mole-rats? Identify and list four such interesting abilities possessed by naked mole-rats.

7. Pick one of the characteristics above. Hypothesize in what way the molecules of that mechanism may have had to evolve to allow the adaptation to occur.

Part II – The Role of Metabolism in Hypoxic Survival

In all kingdoms of life, extreme habitats drive adaptive changes to enable species to exploit challenging environments. One challenge faced by subterranean mammals that inhabit confined spaces is that the air is low in O_2 and high in CO_2.

We are going to study the adaptation of naked mole-rats to low O_2 and high CO_2 conditions, as this eusocial rodent combines a subterranean lifestyle with large colony sizes of up to 280 members. CO_2 levels in naked mole-rat burrows can reach 7 to 10%, up to 240 times higher than that in the surface air. Naked mole-rats do not begin to display behavioral avoidance, hyperventilation, or tissue acidosis to this superabundance of CO_2 until its level reaches 10%, a level that may cause convulsions, coma, and death in a typical mammal (e.g., humans). Even a five-hour exposure to 80% CO_2 (20% O_2) was not lethal for naked mole-rats, as it would be in most other mammals. O_2 levels are low in the burrows of subterranean mammals (as low as 6%, compared to normal air at 21%), and the mass huddling behavior of naked mole-rats may exacerbate their exposure to hypoxic air. The naked mole-rat can tolerate these extreme levels that are so low in oxygen that they would cause brain damage and death in other mammals including humans. Recent studies revealed that the resistance of naked mole-rats to hypoxia has something to do with the enzyme aldolase. We will review the role of aldolase in the context of glycolysis.

Questions

1. Hypoxia occurs when an organism does not have access to enough oxygen. List some of the problems that lacking oxygen may have on a mammal.

2. Why is the presence of high concentrations of CO_2 bad for an organism? List at least three consequences of a mammal being in an environment with high CO_2 levels. Focus on metabolism in answering this question.

3. List all the reactions that aldolase can catalyze.

4. How many different types of Class I aldolase are available in nature? Briefly explain the differences between the different types. Why might three different versions of aldolase have evolved? Propose a hypothesis.

5. Is aldolase activity oxygen dependent? Justify your answer.

6. Hexokinase and phosphofructose kinase are two regulatory enzymes in glycolysis. How are these two enzymes allosterically regulated?

7. How many ATP molecules are produced from glycolysis if you start with:
   a. 1 molecule of glucose?
   b. 1 molecule of fructose?
   c. 1 molecule of glucose-6-phosphate?
   d. 1 molecule of fructose-6-phosphate?
   e. 1 molecule of fructose-1,6-bisphosphate?
   f. 1 molecule of glucose but triose phosphate isomerase is inhibited?

Part III – Metabolic Assessment

To investigate the molecular mechanisms that allow naked mole-rats to overcome hypoxic stress, scientists subjected them to controlled hypoxia using atmospheric chambers, as approved by local ethics committees.

Watch the following video on how scientists performed the experiment and then answer the questions below:

- *Fascinating Footage of Naked Mole-Rat Surviving Without Oxygen:* <https://youtu.be/znM_ZV1C9z8>

  A demonstration of a naked mole-rat surviving low oxygen conditions led by neurobiologist Thomas Park. Running time: 3:27 min. Produced by Smithsonian Channel, 2019.

Questions

1. Scientists exposed naked mole-rats and regular mice to two conditions: 5% oxygen and 0% oxygen. They then tabulated the survival rates of each organism by measuring their time breathing. Based on Figure 1, what specific conclusions can you draw?

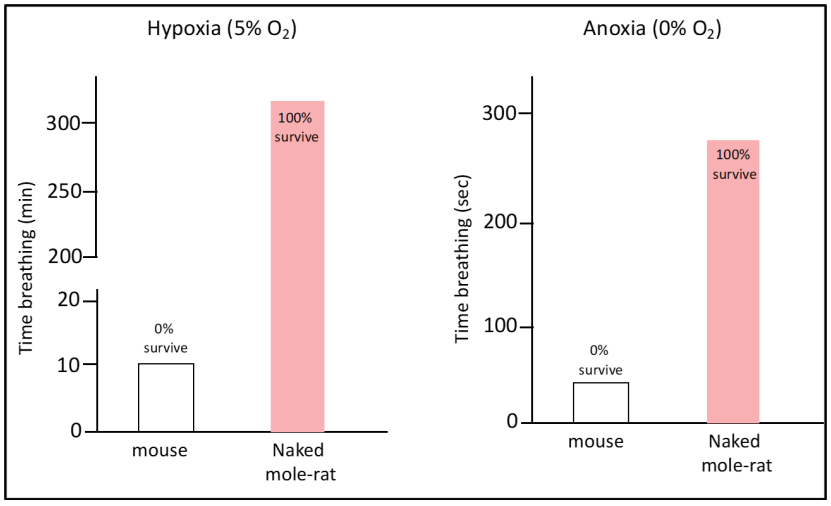

Figure 1. Extreme hypoxia and anoxia resistance in naked mole-rats. Time breathing in 5% O_2 (cut-off time 300 minutes), or in anoxia (0% O_2, cut-off last breath).

2. After the initial results shown in Question 1, scientists wanted to know how long naked mole-rats can survive in 0% oxygen. Figure 2 displays the results they obtained. What are the time limits of survival in 0% oxygen for mice and naked mole-rats?

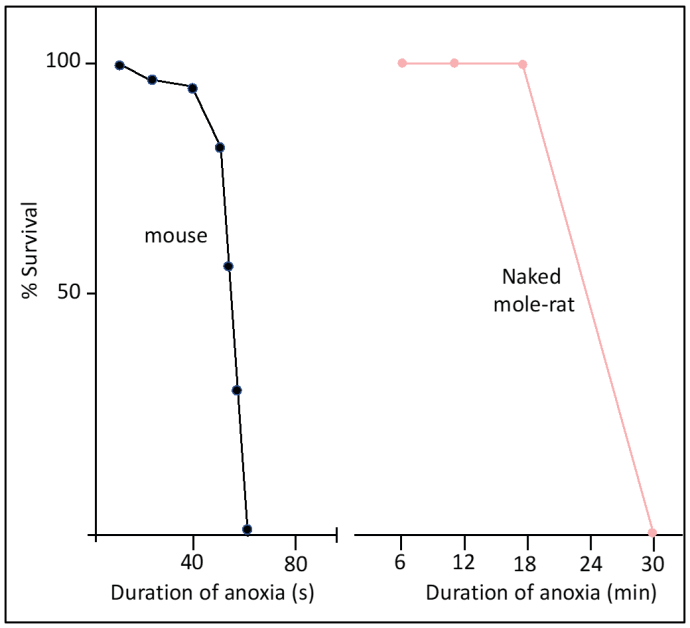

Figure 2. Survival plotted against duration of complete anoxia for mice and naked mole-rats.

3. Scientists postulated that the vital organs of naked mole-rats survive O_2 deprivation by supressing their metabolism in a state of hibernation, torpor, or suspended animation. As a result, the scientists measured the changes in metabolite concentrations during hypoxia and anoxia and compared them to normal conditions.
   a. Why would animals during hibernation suppress their metabolism?

   b. Scientists examined the glucose concentration in various tissues in mice and naked mole-rats. Figure 3 displays the results. Use the figure to answer the questions below.

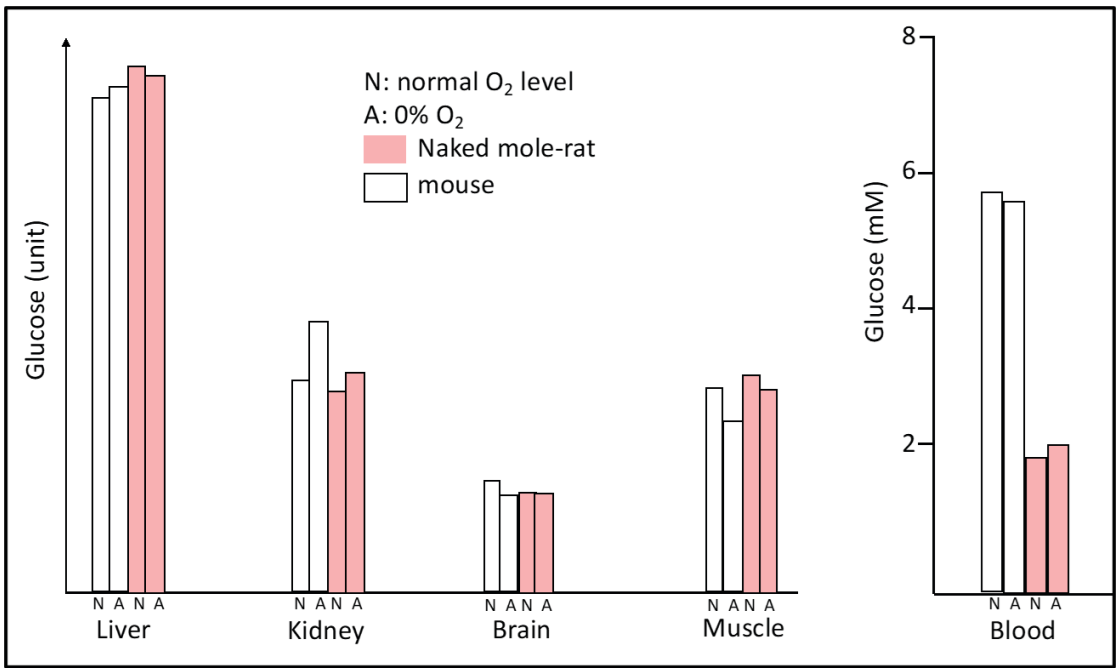

Figure 3. Quantification of glucose levels (concentrations or peak intensity) before and after anoxia.

   i. Why do you think the scientists centered their analysis on the liver, kidney, brain, and muscles?

   ii. Why did the scientists use blood as a control?

   iii. Note the labels of the *x*- and *y*-axis. What are two conclusions that you can draw from these results?

c. Next, scientists examined the fructose, fructose-1-phosphate, and sucrose concentrations in various tissues between mice and naked mole-rats. Figure 4 summarizes the results. Use the figure to answer the questions below.

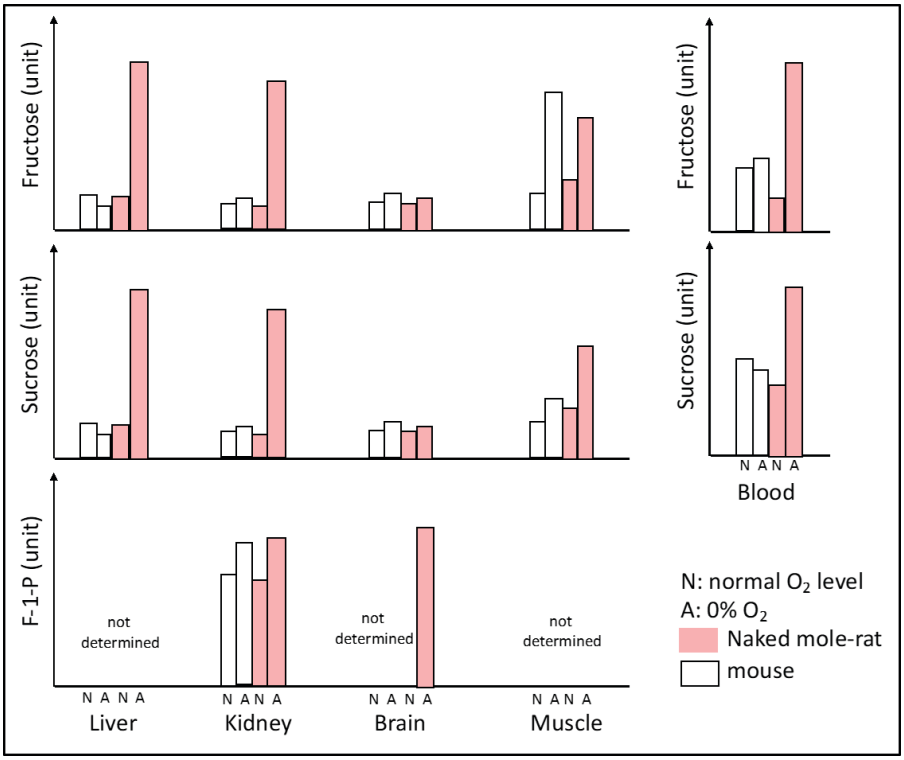

Figure 4. Quantification of fructose, sucrose, and fructose-1-phosphate (F-1-P) levels (concentrations or peak intensity) before and after anoxia.

i. After the initial glucose analysis, hypothesize why the scientists then measured fructose, fructose-1-phopshate, and sucrose levels.

ii. In this experiment, scientists again used the blood sample as a control. However, the result for fructose-1-phosphate level in the blood was not shown. Hypothesize why.

iii. Note the labels of the *x*- and *y*-axis. What are two conclusions you can draw from these results?

5. Scientists reasoned that using fructose, rather than glucose, as an energy source may provide a survival advantage in anoxic environments for naked mole-rats. Based on what you know about how glucose and fructose are metabolized differently, provide an explanation for how fructose-driven glycolysis supports anoxia resistance in the naked mole-rats.

Part IV – Connections to Human Health

Let's review what we have learned by watching the following video:

- *Are Naked Mole-Rats the Strangest Mammals?* <https://youtu.be/2sKADUBfdMk>
  Running time: 4:46 min. Produced by TED-Ed, 2018.

Questions

1. The video mentions that understanding how a mammal can survive in a low oxygen environment could assist stroke victims. What are other possible benefits that might be gained from learning how a mammal can survive in a low oxygen environment?

2. Many of us may feel insecure about our self-perceived weaknesses. Considering the peculiar charactersitics of naked mole-rats, perhaps these so-called weaknesses in our eyes are actually strengths when viewed by others. Can you think of one of your weaknesses that turned out to be one of your greatest strengths?

3. What are your remaining questions from this case study?

Reference

Park, T.J., J. Reznick J., B.L. Peterson, G. Blass, D. Omerbašić, ..., & G.R. Lewin. (2017). Fructose-driven glycolysis supports anoxia resistance in the naked mole-rat. *Science* 356(6335): 307–11. <https://doi.org/10.1126/science.aab3896>