



Published in final edited form as:

Science. 2017 April 21; 356(6335): 248–249. doi:10.1126/science.aan1505.

Rewiring metabolism under oxygen deprivation:

Naked mole-rats evolved a means to cope with anoxia

Jay F. Storz¹ Grant B. McClelland²

¹School of Biological Sciences, University of Nebraska, Lincoln, NE 68588, USA.

²Department of Biology, McMaster University, Hamilton, ON L8S 4K1, Canada.

When faced with a reduced availability of oxygen in the environment (hypoxia), vertebrates can make a variety of respiratory, cardiovascular, and hematological adjustments to ensure an uninterrupted supply of oxygen to the cells of metabolizing tissues (1, 2). These are adaptive solutions for “aerobic organisms in an aerobic world” (3). Coping with the complete absence of oxygen (anoxia) requires more fundamental alterations of cellular metabolism that are typically nothing more than emergency stopgap measures to buy time until the oxygen supply is (hopefully) reestablished (4). On page 307 of this issue, Park *et al.* (5) identify a new champion of anoxia tolerance among mammals— the naked mole-rat.

The mammalian brain is especially sensitive to oxygen deprivation because of its high mass-specific rate of energy metabolism, which is fueled by plasma-derived glucose as a carbon and energy source. Because the delivery of glucose and oxygen to neurons is closely coupled to energy demand, oxygen in the brain lasts for only seconds after the cessation of blood flow, and the supply of the energy-carrying molecule adenosine triphosphate (ATP) is depleted within 1 to 2 min (6). When the ATP supply is no longer sufficient to maintain cellular ion homeostasis, depolarization of cell membranes leads to necrotic or apoptotic cell death (4, 7). Consequently, most vertebrates can survive for no more than a few minutes under anoxia.

There exist, however, a few ectothermic vertebrates that can survive for months under complete anoxia. These include North American freshwater turtles (genera *Trachemys* and *Chrysemys*) and Eurasian cyprinid fishes (genus *Carassius*), such as the crucian carp and the goldfish, which overwinter in the anoxic waters of ice-covered lakes and ponds (4). These facultative anaerobes dramatically depress their metabolism and body temperature, enabling them to survive on anaerobic fuel stores (glycogen) in a state of suspended animation or drastically reduced activity. No endothermic vertebrates come close to matching these extreme levels of anoxia tolerance.



The naked mole-rat survives anoxia by switching to fructose-based anaerobic metabolism.

Naked mole-rats (*Heterocephalus glaber*) cope with an atmosphere of extremely low oxygen and high carbon dioxide in their subterranean burrow systems (see the photo). Because every aspect of naked mole-rat biology seems to be unusual and bizarre in some way, it is perhaps not surprising that they have evolved a particular means of tolerating low oxygen conditions. Park *et al.* observed that naked mole-rats can tolerate an atmosphere of 5% oxygen for 5 hours without undue stress, whereas mice (*Mus musculus*) died of asphyxiation in <15 min. Under complete anoxia (0% oxygen), mice and naked mole-rats both quickly lost consciousness. However, whereas mice quickly passed the point of no return and could not be resuscitated even when reexposed to ambient air (21% oxygen) within a minute of the initial anoxia exposure, the naked mole-rats fully recovered from 18 min of complete anoxia. This may not seem like much when compared to turtles or crucian carp, but it is astounding by mammalian standards.

How do naked mole-rats manage to survive for so long under complete anoxia? Like fishes and turtles living under the ice in anoxic ponds, the naked mole-rats dramatically reduce energy turnover to safeguard ATP in the brain and other vital organs. This metabolic suppression is critically important because anaerobic pathways are far less efficient than oxidative phosphorylation for producing ATP. Unlike fishes and turtles, however, naked mole-rats do not maintain large glycogen stores as fuel for prolonged anaerobic metabolism. A clue as to what might be going on was provided by metabolomic profiles of tissues from anoxic naked mole-rats, which revealed extraordinarily high concentrations of the sugar fructose. Using stable isotopes, Park *et al.* confirmed that naked mole-rats substitute fructose for glucose as a fuel for anaerobic metabolism in the brain and heart.

What is the advantage of using fructose to fuel the anaerobic metabolism of vital organs? A switch to fructose has the advantage of bypassing a key regulatory step that limits glycolytic flux. Glucose metabolism is tightly regulated by phosphofructokinase, a flux-controlling step that is subject to feedback inhibition by ATP, hydrogen ions, and citrate. By entering the pathway downstream of phosphofructokinase, fructose metabolism can continue under conditions when glycolysis would normally grind to a halt. Like a cab driver taking a back-road detour around stopped traffic, this rewiring of metabolism permits continued flux through glycolysis independent of the energy status of the cell. This metabolic innovation

required naked mole-rats to recruit appropriate fructose transporters and enzymes for expression in the brain and heart, as they are normally only expressed in the kidney.

A serious problem with the acceleration of anaerobic pathways for ATP production is the associated production of lactate as an end product. Anoxia-tolerant fishes and turtles have evolved solutions to this problem (4). In anoxia, goldfish and carp export metabolically produced lactate to skeletal muscle where it is converted to ethanol, which then diffuses from the gills into the water. Anoxia-tolerant turtles lack the ability to produce alternative anaerobic end products, so they instead evolved a distinct means of buffering excess lactate and hydrogen ions in the blood by releasing calcium carbonate from their shells. Neither of these exotic mechanisms would be available to mammals, so it will be interesting to find out how the naked mole-rats have evolved their own solution to the problem of lactate clearance. One possibility is that their ability to maintain cardiac function in anoxia facilitates the circulatory clearance of lactate from active tissues. Such possibilities highlight the value of having a mammalian model for studying anoxia tolerance.

Glycolysis is an ancient metabolic pathway and is highly conserved among vertebrates, so it is surprising that an evolutionary modification of pathway circuitry has contributed to the remarkable physiological capacities of naked mole-rats. The adaptations of these enigmatic mammals also have potential biomedical relevance, as insights into their previously unknown metabolic capacities and protective mechanisms may help guide the design of strategies to mitigate anoxic tissue damage caused by ischemic heart disease or stroke, conditions that are leading causes of death worldwide (8).

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