Mice Can Sense Oxygen Through Skin

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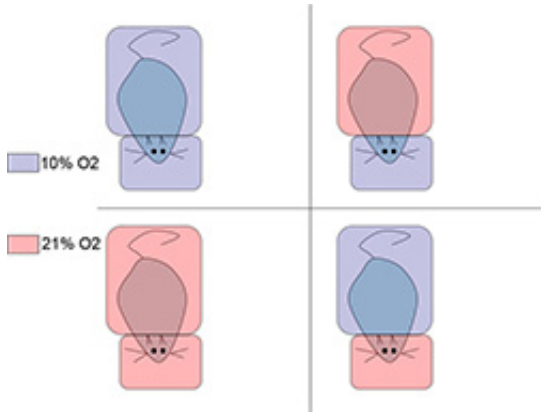

Researchers exposed the head and bodies of the mice separately to mixtures of 10 percent oxygen—about the level found at Mt. Everest—and 21 percent oxygen, found at sea level. Credit: UC San Diego

Biologists at the University of California, San Diego have discovered that the skin of mice can sense low levels of oxygen and regulate the production of erythropoietin, or EPO, the hormone that stimulates our bodies to produce red blood cells and allows us to adapt to high-altitude, low-oxygen environments.

Their surprising finding, published in the April 18th issue of the journal *Cell*, contradicts the notion of mammalian skin as an envelope around our bodies with little connection to the respiratory system.

If found to apply to humans, the discovery could radically change the way physicians treat anemia and other diseases that require boosting our

bodies' ability to produce red blood cells. It also could be used to improve the performance of endurance athletes competing in this summer's Olympic Games.

"What we found in this study is really something quite unusual," said Randall Johnson, a professor of biology at UC San Diego who headed the research study. "We discovered that mammalian skin, at least in mice, responds to how much oxygen is above it and, by virtue of that response, changes blood flow through the skin. This, in turn, changes one of the most basic responses to low oxygen that we have, which is the production of erythropoietin."

Those responses, the researchers suspect, could be ancient traits retained as mammals evolved from lower forms of vertebrates, such as amphibians, that possess the same sorts of ion channels to promote oxygen diffusion in their extremely permeable skins as mammals have in their lungs.

"Amphibians—frogs most notably—breathe through their skin and are able to sense and respond to how much oxygen is in the air or water around their skin," Johnson added. "But nobody had ever thought about asking those questions about the skin of mammals."

"From an evolutionary point of view, the results make sense, considering the important role of the skin for oxygen uptake in amphibians," said Frank Powell, a professor of medicine at UCSD and expert in human and animal adaptations to high-altitude environments who was part of the team. "It will be very interesting to see how these mechanisms work in humans and if, for example, different oxygen levels at the skin could affect how rapidly and how well one adapts to low oxygen in the intensive care unit of a hospital or at high altitude."

The UC San Diego team found no evidence that mice could breathe

through their skin. But if their discovery that mice sense low oxygen through their skin and trigger EPO production is found to apply to humans, it would have dramatic implications for the training and testing of endurance athletes during the Summer Olympic Games in Beijing.

Besides training at altitude and in low-oxygen tents—the two generally accepted legal methods of boosting red blood cell production--runners, swimmers, cyclists and other endurance athletes seeking better performances by increasing the oxygen-carrying capacity of their blood may now have another legitimate way to increase their red blood counts. Blood doping, the injection of additional red blood cells into the body, and the injection of synthetic recombinant EPO to boost red blood cell production are illegal in the Olympics and banned by most sports governing bodies. But what if athletes could boost their own EPO and red blood cell counts by exposing their bodies to low levels of oxygen" Or, to obtain the same effect, by merely increasing blood flow through their skin"

“We’ve discovered a potent physiological trigger that can be enacted or enabled without exogenous sources of EPO,” said Johnson. “We show in this paper that breathing in one level of oxygen and exposing your body to another level of oxygen is really a potent trigger for the body to produce its own EPO. It’s not hard to foresee people taking what we’ve learned in mice and applying it to humans.”

If human skin is found to be sensitive to oxygen levels, it could revive the debate over the “Goldfinger Syndrome.” This idea, perpetuated by the famous James Bond movie in which the villain’s girlfriend is killed after being painted gold, has been the focus of urban legends and internet discussions about the possible negative health effects of painting the skin. It has been the subject of two investigations by the Discovery Channel show “MythBusters.”

The team's discovery—aided by collaborators in Sweden, Germany and the University of Pennsylvania—came after two years of trying to determine why certain mice the researchers had genetically engineered for experiments exhibited high levels of EPO. In 2004, Johnson and his students published a paper in the journal Plos Biology, detailing how they had transformed ordinary laboratory mice into the rodent equivalent of Olympic endurance athletes. They did this by deleting a gene that allows mammalian muscles to switch from aerobic to anaerobic metabolism when oxygen levels in the muscle run low.

Most of our daily activities are performed aerobically, through biochemical mechanisms in our muscles that make full use of oxygen. But when the demands of our muscular system exceed its available supply of oxygen, as in sprinting for a bus or lifting a heavy object, a protein known as hypoxia inducible transcription factor-1, or HIF-1, is activated. This protein enables the muscle to switch to the more energetically explosive, but expensive anaerobic process, which does not use oxygen and generates lactic acid as its byproduct.

When Johnson and students knocked out the negative regulator of the HIF-1 gene, they produced tiny mice with skin that look red and flushed. These mice have trouble retaining body heat because a larger proportion of their blood is sent to their skin and cooled, much like a person sitting in a hot sauna or Jacuzzi. But the most puzzling aspect of these mutant mice is their extremely high EPO levels—so high that 90 percent of their blood plasma is composed of red blood cells, compared to 40 to 50 percent for normal individuals.

"Their blood is basically paste and their hearts are enlarged as a result," Johnson said. "We could not understand why the skin was exerting this effect. It just didn't make sense to us. We could figure out every other aspect of why this mutant mouse looked an acted the way it did, but this one thing was really bothersome to us, so that sent us down this road.

When we found that the EPO was coming from internal organs, not the skin of these mice, we thought there must be some kind of signal from the skin to the internal organs."

Johnson and others in his laboratory—graduate student Adam Boutin, postdoctoral fellow Alexander Weidemann and undergraduate Lernik Mesropian—verified that the HIF-1 gene was responsible by genetically engineering mutant mice without the gene in their skin cells. These mice were unable to signal the production of extra EPO when their skin was exposed a chamber filled with 10 percent oxygen—about the level found at Mount Everest. The concentration of oxygen at sea level is about 21 percent. Normal mice were able to increase the amount of EPO production at this 10 percent level.

This occurred, the researchers found, when more blood rushed into the skin. By putting on the mouse's skin a nitroglycerine patch, which increases blood flow through the skin, the researchers found that mice could dramatically increase their production of EPO and red blood cells.

"EPO administration is a multi-billion dollar drug market for the treatment of all sorts of diseases involving low red blood cell counts," said Johnson. "So the ability to manipulate red blood cell production just by changing blood flow through certain parts of the skin could be profound. We show in this study that by just putting a little nitroglycerine patch we were able to trigger very big increases in EPO. Whether this turns out to be true for humans, we don't know yet. But potentially this could be a very interesting way to manipulate this pathway."

Johnson and his team, which included UCSD assistant professor of biology Colin Jamora, found that having mice breathe in a chamber with their entire bodies exposed to low levels of oxygen had the greatest response and produced the most EPO. When the mice were allowed to

breathe 10 percent oxygen in one chamber, but had the skin from their neck down exposed to 21 percent, or sea-level oxygen, in another chamber built by Powell, more than one-half of their adaptation to low oxygen was lost.

“If we put mice that lack a hypoxic response in their skin in a low oxygen chamber more than half of their hypoxic response goes away and that was surprising to us,” Johnson said. “The skin really is a big contributor to the way the mouse responds to low oxygen.”

“All of the important responses to hypoxia, or low oxygen, were thought to be triggered by oxygen-sensitive nerves and molecules in the blood and internal organs,” said Powell. “However, these experiments clearly show that the skin directly responds to changes in oxygen in the environment with changes in blood flow. These changes in skin blood flow are highly significant by causing changes in the levels of hypoxic inducible factor, which is a sort of ‘master switch’ for adapting to low oxygen that activates multiple genes to enhance oxygen delivery throughout the body.”

Johnson said that because people with skin inflammations such as psoriasis and eczema can have low red blood cell counts, he and his team are interested in extending their study to investigate anemia caused by skin inflammations in their mutant mice.

“In people with anemia of inflammation it seems as if the EPO isn’t having an effect,” he added. “We actually have mutant mice with skin inflammation that show this same effect. They have high EPO levels, but they don’t have a high red blood cell count. The mutants we used in our study have high EPO levels and high red blood cell counts. But they don’t have inflammation. The next step for us is going to be trying to figure out why these inflammatory diseases trigger EPO. Is there something about inflammation that we can trigger so these people can be

treated without suffering this kind of anemia""

The scientists said in their paper that their discovery also might explain why people in some parts of Nepal, India and Pakistan massage newborn babies in mustard oil, a mild irritant that promotes blood flow through the skin.

“We show in this study that if you paint the skin of a mouse with this mild irritant, mustard oil, it will also trigger EPO release at a somewhat lower level,” Johnson said. “In India and Pakistan babies are in some communities massaged in mustard oil at birth; and some health workers have been trying to get them to stop this folk tradition. But we show that in mice this increases EPO levels. And since increased EPO levels contribute to increased red blood cell counts one could imagine it being beneficial.”

Source: University of California - San Diego