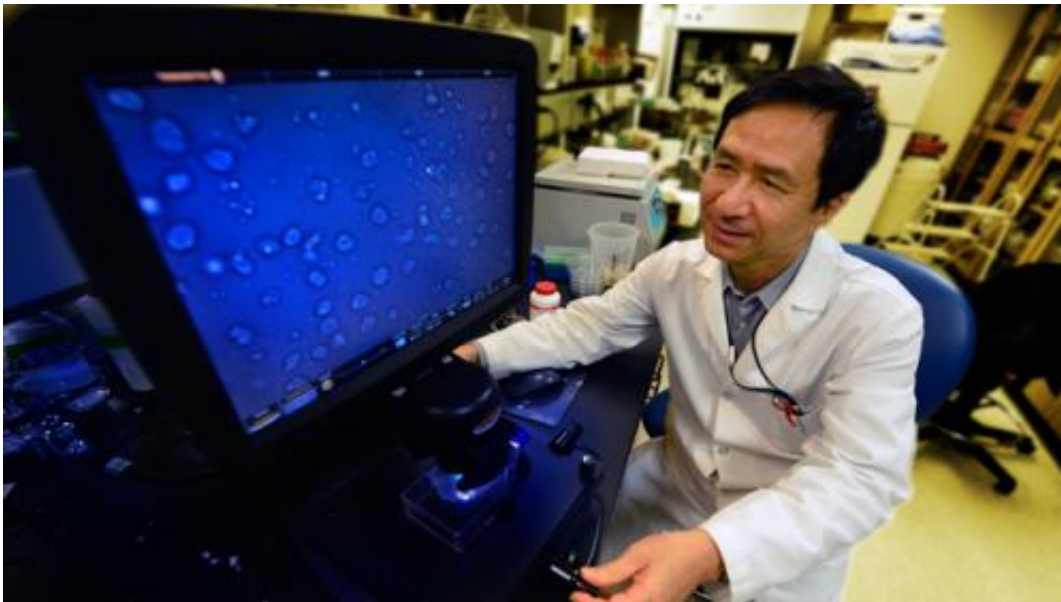


Low levels of oxygen, nitric oxide worsen sickle cell disease

March 20 2014



This is a photo of Dr. Tohru Ikuta, a molecular hematologist at the Medical College of Georgia at Georgia Regents University. Credit: Phil Jones

Low levels of both oxygen and the powerful blood vessel dilator nitric oxide appear to have an unfortunate synergy for patients with sickle cell disease, researchers report.

Their studies indicate that the two conditions common in sickle cell disease, dramatically increase red [blood cells](#)' adhesion to the lining of blood vessels walls and the debilitating pain crises that can result.

The good news is that restoring normal levels of [nitric oxide](#) can substantially reduce red blood [cell adhesion](#), said Dr. Tohru Ikuta, a molecular hematologist at the Medical College of Georgia at Georgia Regents University. Ikuta and Dr. C. Alvin Head, former Chairman of MCG's Department of Anesthesiology and Perioperative Medicine, are co-corresponding authors of the study in the journal *Blood*.

The study also points to a potentially new therapeutic target, the self-adhesion molecule P-selectin, which the researchers found played a central role in increased red blood cell adhesion. Low levels of oxygen and nitric oxide both increase expression of P-selectin.

Hypoxia, or low oxygen levels, can strike anyone in the face of, for instance, the flu, a bad cold, strenuous exercise or exposure to high altitudes. Additionally, sickle cell [patients](#) can have chronic problems with oxygen delivery.

Oxygen is carried in hemoglobin, which travels the bloodstream to its target tissue inside typically flexible, oval-shaped red blood cells. The sickled shape of the hemoglobin in sickle cell disease can impede the journey and often results in oddly shaped, fragile red blood cells as well, said Ikuta. These red blood cells can spill their contents into the bloodstream, where oxygen readily binds with the nitric oxide and patients quickly find themselves with insufficient levels of both.

To understand the relationship between low levels of oxygen and nitric oxide, researchers infused sickled red blood cells into mice incapable of producing nitric oxide. The cells immediately began sticking to blood vessel walls, while normal mice were unaffected. In the face of low oxygen levels, or hypoxia, cell adhesion increased significantly in the nitric oxide-deficient mice.

"It's a synergy," Ikuta said. "This shows that hypoxia and low nitric oxide

levels work together in a bad way for sickle cell patients."

When they restored normal nitric oxide levels by having mice breathe in the short-lived gas – as patients have done in clinical trials – cell adhesion did not increase when oxygen levels decreased. Interestingly, there was no additional benefit from increasing nitric oxide levels beyond normal. Rather, restoring normal nitric oxide levels appears the most efficient, effective way to reduce [red blood cell](#) adhesion, the researchers write.

Clinical trials of nitric oxide therapy to ease pain in sickle cell patients have yielded conflicting results, with some patients reporting increased pain. The new findings and the fact that patients with [sickle cell disease](#) have significant variability in their nitric oxide levels – even during a pain crisis – likely explains why, Ikuta said.

Nitric oxide therapy likely would benefit only patients with intermittent or chronically low levels, he said. "The answer is that some patients may not need this. And, our studies indicate that there is no therapeutic benefit to increasing levels beyond physiologic levels."

Nitric oxide blood levels can be readily measured, he noted, and are more likely to drop in every patient during a pain crisis.

Provided by Medical College of Georgia

Citation: Low levels of oxygen, nitric oxide worsen sickle cell disease (2014, March 20) retrieved 5 May 2024 from

<https://medicalxpress.com/news/2014-03-oxygen-nitric-oxide-worsen-sickle.html>

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