Study confirms controversial nitrite hypothesis

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Understanding how nitrite can improve conditions such as hypertension, heart attack and stroke has been the object of worldwide research studies. New research from Wake Forest University has potentially moved the science one step closer to this goal.

In a paper published online ahead of print in the February issue of the Journal of *Biological Chemistry*, senior co-author Daniel Kim-Shapiro, professor of physics at Wake Forest, and others show that deoxygenated hemoglobin is indeed responsible for triggering the conversion of nitrite to nitric oxide, a process that affects blood flow and clotting.

"We have shown that conversion of nitrite to nitric oxide by deoxygenated hemoglobin in red blood cells reduces platelet activation," Kim-Shapiro said. "This action has implications in treatments to reduce clotting in pathological conditions including sickle cell disease and stroke."

In 2003, Kim-Shapiro collaborated with Mark Gladwin, now at the University of Pittsburgh, who led a study that showed that nitrite (which is also used to cure processed meats), is not biologically inert as had been previously thought, but can be converted to the important signaling molecule nitric oxide (NO), and thereby increase blood flow. At that time, the researchers hypothesized that the conversion of nitrite to NO was due to a reaction with deoxygenated hemoglobin in red blood cells.

The main goal of the latest research, Kim-Shapiro said, was to determine

how red blood cells perform these important signaling functions that lead to increased blood flow. The researchers used several biophysical techniques to measure NO production from nitrite and red blood cells and examined the mechanism of NO production.

"Importantly, this action was increased under conditions of low oxygen - so nitrite acts to increase blood flow in the body just when it is needed. What we're showing with this research is what part of the red cell is doing this, and it's consistent with our original hypothesis," he said. "This speaks to the mechanisms and how they work - to how nitrite is dilating blood vessels and reducing clotting."

As director of Wake Forest University's Translational Science Center, Kim-Shapiro and others have conducted studies that look at how nitrite and its biological precursor, nitrate (found in beet root juice) can be utilized in treatments for a variety of conditions. In a 2010 study, they were the first to find a link between consumption of nitrate-rich beet juice and increased blood flow to the brain.

Kim-Shapiro said that next steps in the research include examining whether all red blood cells have this activation function and whether this function is diminished in red cell diseases like sickle cell disease, other blood diseases, or in the transfusion of older blood.

"Does this important function that we can now attribute to the hemoglobin in the red cells get compromised under certain conditions? And if so, how can we enhance it?" he said.

Provided by Wake Forest University