Discovery of nitric oxide delivery mechanism may point to new avenue for treating high blood pressure

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(Medical Xpress)—Researchers at the University of Virginia School of Medicine have shed new light on blood pressure regulation with the discovery of an unexpected mechanism by which hemoglobin controls the delivery of nitric oxide. The findings may point to a new therapeutic target for treating high blood pressure and may have far-reaching implications for many organ systems and illnesses.

Hemoglobin is best known for its role in transporting oxygen in the blood. But it also can bind nitric oxide, a powerful vasodilator. By relaxing smooth muscle cells, nitric oxide widens blood vessels, decreasing blood pressure. The new U.Va. research shows that there is a complete system within the myoendothelial junction – the "bridge" between the smooth muscle and the endothelial cells lining the blood vessel walls – that allows hemoglobin to regulate nitric oxide delivery, essentially controlling the size of the blood vessel.

The U.Va. researchers were surprised to spot hemoglobin alpha in the myoendothelial junction. At first they thought it was a mistake. "We didn't believe it. We thought it was contamination," said researcher Brant Isakson, an associate professor of molecular physiology and biological physics. "Maybe we had a blood smear on our fingers? … Then we started to put two and two together."

What they found has earned them a place in the pages of the prestigious

journal *Nature*.

The U.Va. team had seen reports of hemoglobin alpha from other researchers looking at myoendothelial junctions. But it would typically be one protein in a list of many, reported for the sake of completeness. The U.Va. researchers, however, realized hemoglobin alpha was actually regulating the binding of nitric oxide, directly affecting the size of the blood vessel.

"To make a complicated story short, we did find it binds the nitric oxide, and it can bind it very tightly or loosely," Isakson said. "Basically, what we have in this very localized structure is a complete system for regulating nitric oxide delivery to the smooth muscle."

Some chronic problems with high blood pressure, Isakson suspects, may be the result of problems with the amount of hemoglobin in the blood vessel wall.

"The implications for this research are very widespread. The most immediate thing is blood pressure regulation," Isakson said. "We're trying to find ways to specifically delete hemoglobin alpha in the blood vessel wall and look at blood pressure changes."

But the mechanism the U.Va. researchers have identified may play an important role in many other parts of the body, and possibly in many illnesses. "There are all these scattered reports of hemoglobin and [nitrogen oxide signaling] expressed in the lungs, for example, and in neurons, and in all these other places. Maybe, just maybe, it's very similar to what we show here: That they form this macromolecular complex and that can very tightly regulate how much nitric oxide is delivered," Isakson said.

"In our case, we're very interested in how that nitric oxide regulates

blood pressure and dilates the smooth muscle. But you can extrapolate that to neurons. Neurons use nitric oxide for their cell communication," he said. "Inflammatory responses, there's another big one. Nitric oxide is anti-inflammatory. We're really extrapolating here, but if we are correct, if you can regulate how much nitric oxide is released by this complex, then you can regulate the inflammatory response."

More information: The findings have been published by *Nature* online and will appear in a forthcoming print edition.

Provided by University of Virginia