Blood vessels 'sniff' gut microbes to regulate blood pressure

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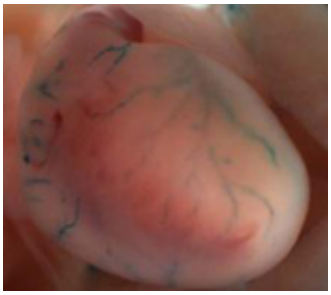

A blue dye marks the presence of olfactory receptor 78 in blood vessels in a mouse's heart. Credit: Jinah Han and Anne Eichmann, Yale University

Researchers at The Johns Hopkins University and Yale University have discovered that a specialized receptor, normally found in the nose, is also in blood vessels throughout the body, sensing small molecules created by microbes that line mammalian intestines, and responding to these molecules by increasing blood pressure. The finding suggests that gut bacteria are an integral part of the body's complex system for maintaining a stable blood pressure.

A description of the research, conducted in mice and test tubes, appeared online Feb. 11 in the journal Proceedings of the National Academy of Sciences.

"The contribution that gut microbes apparently make to blood pressure

regulation and human health is a surprise," says Jennifer Pluznick, Ph.D., assistant professor of physiology at the Johns Hopkins University School of Medicine. "There is still much to learn about this mechanism, but we now know some of the players and how they interact," she adds.

Pluznick says that several years ago, thanks to a "happy coincidence," she found—in the kidney—some of the same odor-sensing proteins that give the nose its powers. Focusing on one of those proteins, olfactory receptor 78 (Olfr78), her team specifically located it in the major branches of the kidney's artery and in the smaller arterioles that lead into the kidney's filtering structures. Olfr78 also turned up in the walls of small blood vessels throughout the body, she says, particularly in the heart, diaphragm, skeletal muscle and skin.

To figure out which molecules bind and activate Olfr78, the scientists programmed cells to have Olfr78 protein receptors on their surface. They also gave these same cells the ability to start a light-producing chemical reaction whenever Olfr78 is activated. By adding different cocktails of molecules to the cells and measuring the light the cells produced, they homed in on a single mixture that activated Olfr78. They then tested each component in that mix and found that only acetic acid (a.k.a. vinegar) bound Olfr78 and caused the reaction.

Acetic acid and its alter ego, acetate, are part of a group of molecules known as short chain fatty acids (SCFAs). When the team tested other molecules in this group, they found that propionate, which is similar to acetate, also binds Olfr78. In the body of mammals, including humans, SCFAs are made when zillions of bacteria lining the gut digest starch and cellulose from plant-based foods. The SCFAs are absorbed by the intestines into the blood stream, where they can interact with Olfr78.

To pinpoint the effect of Olfr78, the scientists gave SCFAs to mice missing the Olfr78 gene and found that the rodents' blood pressure

decreased, suggesting that SCFAs normally induce Olfr78 to elevate blood pressure. However, when they gave SCFAs to normal mice with intact Olfr78, they did not see the expected increase in blood pressure, but rather a decrease, though it was less pronounced than before.

To test the effect of reducing the SCFAs available to Olfr78, the team gave mice a three-week course of antibiotics to wipe out the gut microbes responsible for SCFA production. In this case, normal mice showed very little change in blood pressure, but mice without Olfr78 experienced an increase in blood pressure, suggesting that there were other factors involved in the Olfr78/SCFA/blood pressure relationship.

The mystery was solved, Pluznick says, when the team examined mice lacking Gpr41, a non-smell-related protein receptor located in blood vessel walls that also binds SCFAs. When SCFAs bind to Gpr41, blood pressure is decreased. The researchers eventually discovered that Olfr78 and Gpr41 both are activated by SCFAs, but with contradictory effects. The negative effect of Gpr41 is counterbalanced by the positive effect of Olfr78, but Gpr41's effect is stronger, so an increase in SCFAs produces an overall decrease in blood pressure.

"We don't have the full story yet," says Pluznick. "There are many players involved in the maintenance of stable levels of blood pressure, and these are just a few of them. We don't know why it would be beneficial for blood pressure to decrease after eating or why gut microbes would play a part in signaling that change. But our work opens the door for exploring the effects of antibiotic treatments, probiotics and other dietary changes on blood pressure levels in mice, and perhaps eventually people."

More information: Link to article in *PNAS*: dx.doi.org/10.1073/pnas.1215927110

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