Researchers discover new, treatable pathway known to cause hypertension in obese people

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There's no question that as body weight increases, so too does blood pressure. Now, in a study of mice, Johns Hopkins researchers have revealed exactly which molecules are likely responsible for the link between obesity and blood pressure. Blocking one of these molecules—a signaling channel that's found in a tiny organ on the side of your

neck—effectively lowers blood pressure in obese mice, the researchers reported recently in the journal *Circulation Research*.

"Obesity leads to a lot of bad cardiovascular outcomes, and a significant portion of those are related to poorly controlled blood pressure," says Vsevolod Polotsky, M.D., Ph.D., professor of medicine at the Johns Hopkins University School of Medicine and a senior author of the new paper. "We've identified what may be a new way to lower blood pressure in obese patients and improve these outcomes."

Nearly a third of American adults have high blood pressure, and only about half of those people have their blood pressure under control through medications and lifestyle changes. Hypertension can be especially difficult to treat in obese patients, Polotsky says.

The new work revolves around leptin, a molecule that controls appetite and metabolism in response to food. Obese people often become resistant to leptin, so rising levels of the molecule after a meal no longer boost metabolism or cause a feeling of fullness. In response to this resistance, leptin levels continue to rise with obesity. Leptin has also been shown to increase blood pressure and, surprisingly, obesity doesn't change that link—even when people are resistant to leptin's effects on metabolism and appetite, their blood pressure rises in response to the molecule. Until now, researchers weren't sure why.

"It didn't make a lot of sense why obese people were only resistant to some of the effects of leptin," says Polotsky. "It suggested to us that maybe leptin was having a peripheral effect outside the brain."

Previous studies had revealed that there were high levels of leptin receptors in the carotid bodies—tiny clusters of cells along the carotid arteries on either side of the throat that respond to changing levels of oxygen and carbon dioxide in the blood. Polotsky wondered whether this

could be where leptin affects blood pressure, completely separate from its effects on appetite and metabolism in the brain.

Blood pressure is measured in millimeters of mercury (mm Hg) and has two readings—systolic and diastolic. According to the American Heart Association, the risk of dying from a heart attack or stroke doubles with every 20 mm Hg systolic or 10 mm Hg diastolic increase among older adults.

In the new paper, Polotsky's group first confirmed that giving high doses of leptin to lean mice triggered a rise in blood pressure of 10.5 to 12.2 mm Hg, while having no effect on heart rate or food intake. Then, they repeated the experiment in mice without functioning carotid bodies. This time, the animals' blood pressure didn't change in response to leptin. Next, the team studied obese mice that had no leptin receptors—despite their weight, they had normal blood pressure. But when the researchers injected the genes for leptin receptors directly into the carotid bodies of these mice, the animals' blood pressure readings rose by 9.4 to 12.5 mm Hg.

"This is a completely new mechanism of hypertension in obesity," says Polotsky.

After establishing that the carotid body is required for leptin to cause hypertension, the researchers wanted to know what other signaling molecules in the carotid body might be involved. By sifting through previously collected data on what molecules are in the carotid body, they honed in on the transient receptor potential (TRPM7) calcium channel. Polotsky and his team treated mice with the multiple sclerosis drug FTY720 (fingolimod), which blocks channels typically involved in the immune system, including TRPM7 (the drug's mechanism to treat multiple sclerosis is due to blocking a receptor called S1PR1). In this current study, the drug effectively stopped extra doses of leptin from

increasing blood pressure in lean mice, both when given systemically and when applied as a topical gel on the skin directly above the carotid bodies.

"We are now working with biochemists to develop a long-acting drug that acts specifically on TRPM7 in the carotid body," says Polotsky. More research is needed to determine whether such a drug could effectively treat hypertension in obese people.

Provided by Johns Hopkins University School of Medicine

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