Satiety hormone leptin plays a direct role in cardiovascular disease in obesity

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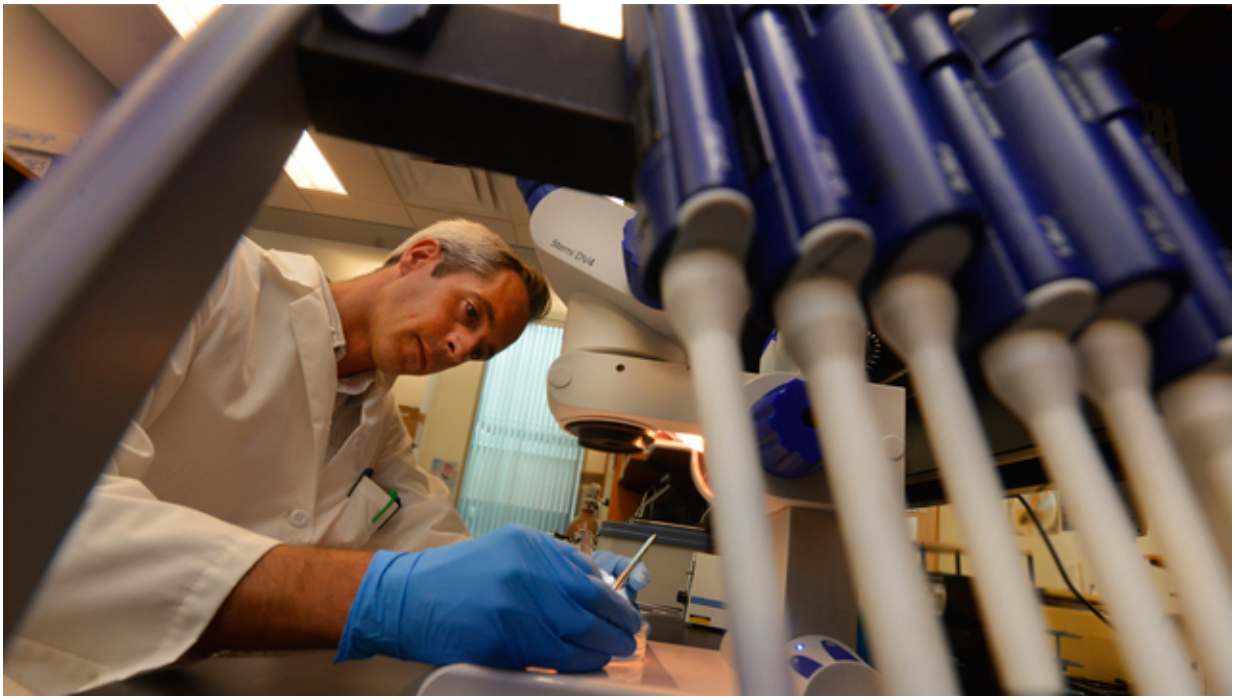

Dr. Eric Belin de Chantemele, physiologist in the Department of Physiology at the Medical College of Georgia at Georgia Regents University. Credit: Phil Jones

While high levels of the satiety hormone leptin don't help obese individuals lose weight, they do appear to directly contribute to their cardiovascular disease, researchers report.

"With obesity, leptin cannot tell our brain to stop eating, but it can still tell our brain to increase the activity of the cardiovascular system," said Dr. Eric Belin de Chantemele, physiologist in the Department of Physiology at the Medical College of Georgia at Georgia Regents University.

In both cell culture and animal models, the researchers have shown that fat-derived leptin directly activates aldosterone synthase expression in the adrenal glands, resulting in production of more of the steroid hormone aldosterone.

High aldosterone levels are known to contribute to widespread inflammation, blood vessel stiffness and scarring, enlargement and stiffness of the heart, impaired insulin sensitivity and more.

Aldosterone, which is produced by the adrenal gland, has a direct effect on blood pressure by regulating salt-water balance in the body. High levels of aldosterone are an obesity hallmark and a leading cause of metabolic and cardiovascular problems. But exactly how it gets high in obesity was a mystery.

Identifying the direct connection of high levels of aldosterone and leptin make either a good treatment target to help avoid cardiovascular disease in obesity, the researchers write in the American Heart Association journal *Circulation*. Their laboratory studies indicate that targeting either disconnects the link and associated cardiovascular problems.

There are already drugs out there that could work, including the old blood pressure drug, spironolactone, that directly targets aldosterone but is rarely used as a frontline blood pressure therapy, said Belin de Chantemele, the study's corresponding author. Spironolactone, a diuretic, helps the kidney eliminate water and sodium but hold onto valuable potassium, according to MedlinePlus. One way it works is by

blocking the receptor to which aldosterone binds. There are also leptin receptor blockers under study for a wide range of problems from obesity to cancer.

It seems a bit of physiological irony that fat makes leptin. In fact, fat from a woman makes even more leptin than the exact same amount of fat from a man, although why remains another mystery. Either way, obese individuals become insensitive to leptin's impact on their metabolic, but not their cardiovascular system. Exactly why the brain becomes insensitive to the metabolic effect is yet another mystery, although there are theories about dysfunctional signaling and resistance by the protective blood-brain barrier to letting leptin in, Belin de Chantemele said.

His interest in leptin as an aldosterone trigger was kindled by a 1999 study by German scientists showing that something in fat cells, or adipocytes, was stimulating aldosterone. The fact that obese individuals have high levels of both aldosterone and leptin has been known. Mice he studied with severe endothelial dysfunction - stiff blood vessels and fibrotic hearts - began to put the two together for him. Because these mice, not surprisingly, had high levels of aldosterone and were also hypersensitive to leptin.

The researchers went back to cell culture and put increasing doses of leptin on adrenal cells. They saw increased levels of aldosterone as a result. When they inhibited the leptin receptor, the increases didn't happen. They did similar studies in fat and lean mice alike, and the association kept showing up: the higher the leptin dose, the higher the aldosterone level. When they used inhibitors of hormones already associated with aldosterone, such as angiotensin II, leptin still increased aldosterone. An exception was that fat mice deficient in leptin receptors did not experience high levels of aldosterone. "It's clearly a direct link between leptin and aldosterone," Belin de Chantemele said.

Now they want to see how well the link holds in humans. He and colleagues Dr. Thad Wilkins, professor in the MCG Department of Family Medicine, and Dr. Miriam Cortez-Cooper, associate professor in the GRU Department of Physical Therapy, are starting to look at leptin-aldosterone interaction and levels in 40 overweight men and women who are not taking any cardiovascular medication. They have early evidence, in humans and animals, that the correlation will be strongest in the females, who make so much more leptin.

"We want to see if we can confirm what we are seeing in mice in the human population," Belin de Chantemele said. "If we see that, that probably tells us a blocker of aldosterone action, such as spironolactone, would be a good treatment particularly for obese females."

He notes that high aldosterone levels in obesity are not associated with the usual suspects: angiotensin II, a hormone known to constrict blood vessels; the steroid hormone cortisol; and the adrenocorticotropic hormone, or ACTH, all are known to control aldosterone secretion. In fact, obesity is often associated with low or usual levels of all these, Belin de Chantemele said.

Provided by Medical College of Georgia