Researchers identify a new treatment for metabolic syndrome

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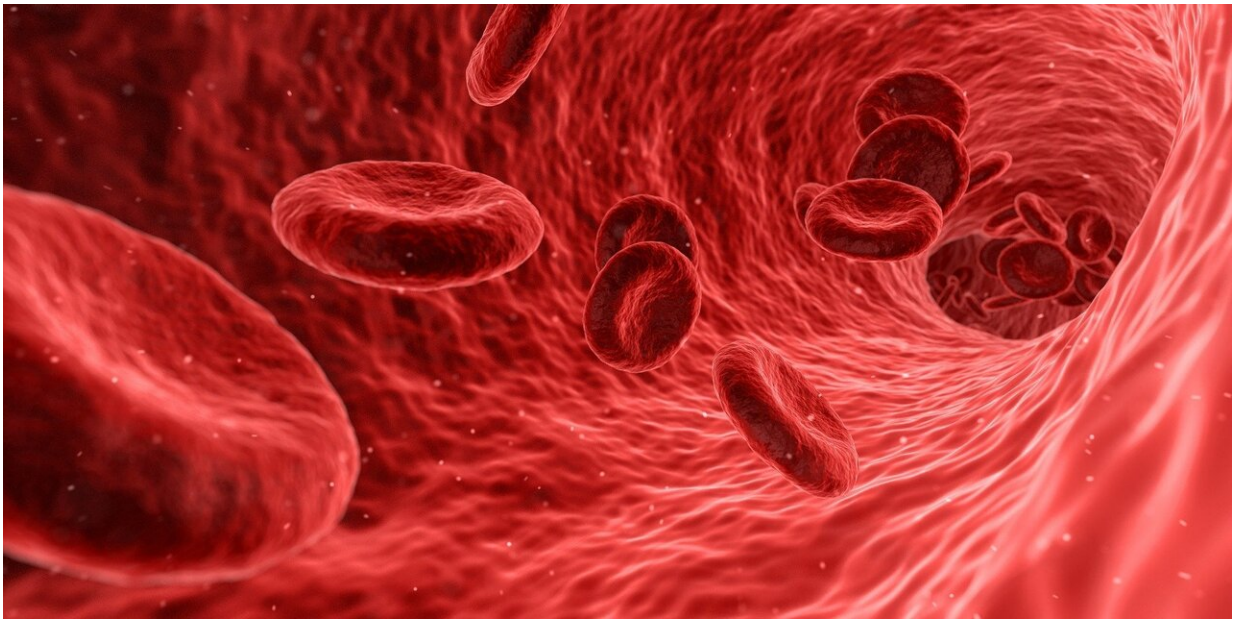

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Metabolic syndrome increases a person's risk for diabetes, heart disease, and stroke, and includes conditions such as obesity, high blood pressure and high blood sugar. In a recent mouse-model study, published in *Cell Metabolism*, researchers at University Hospitals (UH), Harrington Discovery Institute at UH, and Case Western Reserve University have furthered their progress to develop a drug to treat metabolic syndrome by identifying a receptor that controls appetite and body weight.

"In 2016, our lab discovered a hormone called asprosin, which stimulates appetite and increases blood glucose levels by acting on the hypothalamus and the liver," explained Atul Chopra, MD, Ph.D., senior author on the study, Investigator at the Harrington Discovery Institute and Associate Director of the Oxford-Harrington Rare Disease Center, Attending Medical Geneticist at UH, and Associate Professor of Medicine, and Genetics and Genomics at Case Western Reserve School of Medicine. "Individuals that have low blood asprosin levels don't feel hunger like others do and have lower glucose and insulin levels."

Asprosin stimulates appetite by activating key "hunger" neurons of the brain, called AgRP neurons. Asprosin works by binding a protein on the neuron surface called a "receptor." To better understand how receptors work, one might use a key and lock analogy, where a hormone is a key, and its receptor is the lock.

"By using a sophisticated technique called mass spectrometry, we identified protein tyrosine phosphatase receptor δ (Ptprd) as the receptor for asprosin," said Ila Mishra, Ph.D., first author on the study and research associate at Harrington Discovery Institute and Case Western Reserve School of Medicine. "Genetic deletion of Ptprd in mice reduced appetite and body weight, rendering mice unresponsive to asprosin's appetite stimulating effect. In other words, Ptprd is necessary for asprosin-mediated appetite stimulation. This result is the crux of our discovery. A receptor is necessary for a hormone to work, and in the case of asprosin's ability to control appetite and body weight, that receptor is Ptprd."

The identity of the receptor that allows asprosin to activate AgRP neurons and stimulate appetite was previously a mystery, and this gap in knowledge was a barrier to fully understanding how this hormone works.

Since the discovery of asprosin, many studies have shown that blood

asprosin levels are elevated in patients with metabolic syndrome, leading to weight gain and high blood sugar. The research team has also seen that reduced blood asprosin levels lead to protection from metabolic syndrome by suppressing appetite and blood sugar.

"The identification of Ptprd as an asprosin receptor provided us an opportunity to develop a new therapeutic against metabolic syndrome," said Dr. Chopra.

"We used the discovery of the asprosin-receptor to develop a new drug called a receptor trap," explained Dr. Mishra. "This new drug suppressed appetite, body weight and blood glucose levels in obese mice by sequestering plasma asprosin. From a clinical standpoint, it means that this discovery could potentially yield a brand-new drug against metabolic syndrome."

"Further, we believe that asprosin performs many more functions in addition to appetite stimulation," added Dr. Mishra. "Identifying these new functions is the next step in our research."

The team also plans to study intracellular mechanisms involved in asprosin-Ptprd signaling, and simultaneously develop the Ptprd receptor trap for potential use in patients with metabolic syndrome.

More information: Mishra et al, Protein tyrosine phosphatase receptor δ serves as the orexigenic asprosin receptor, *Cell Metabolism* (2022). DOI: 10.1016/j.cmet.2022.02.012

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