Researchers discover a new mechanism that could counteract obesity

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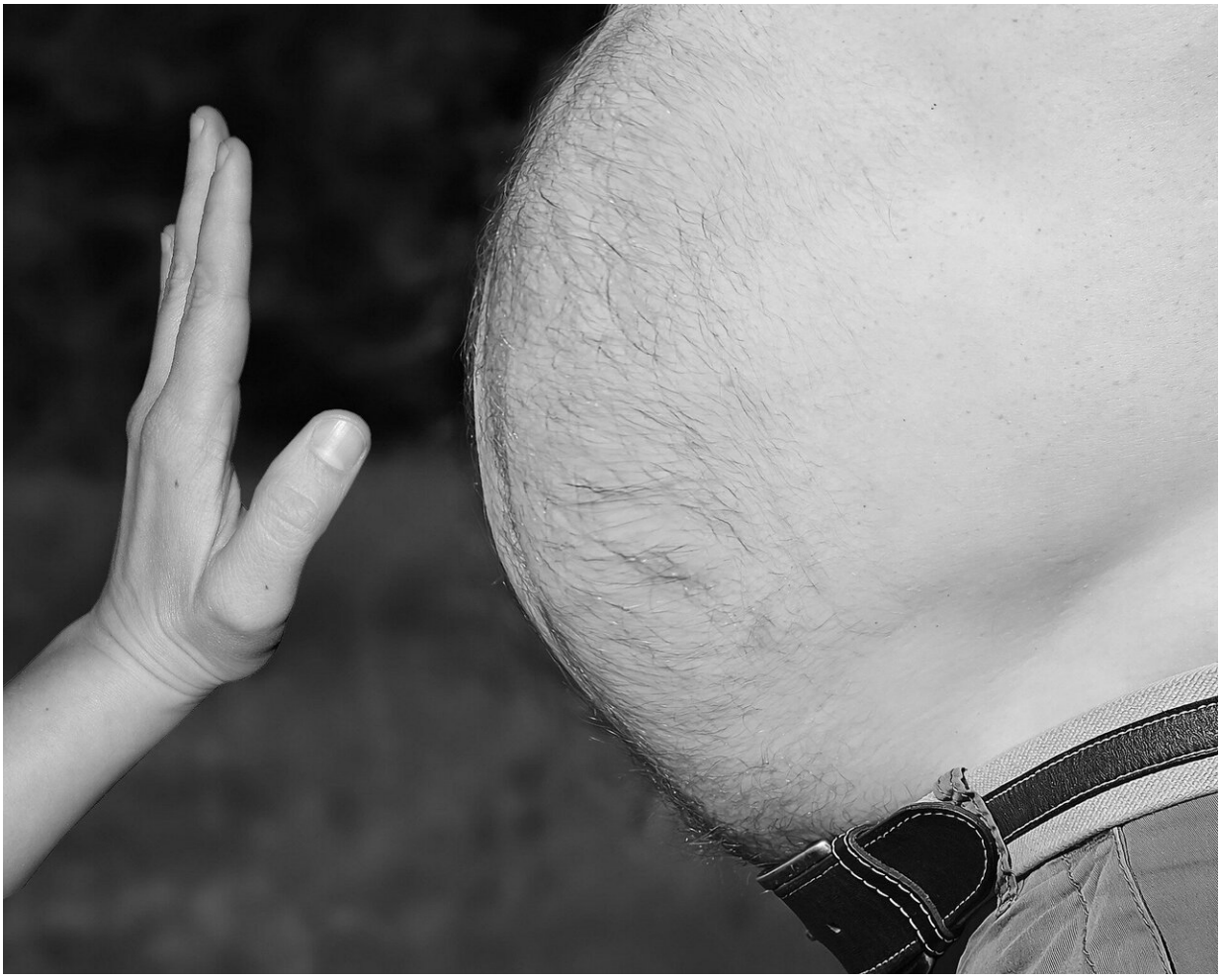

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Obesity rates worldwide have nearly tripled since 1975. Now, new research from the University of Minnesota Medical School has discovered, in rodents, critical mutations in molecules implicated in obesity, which may help inform the development of new anti-obesity therapies.

Lead author Alessandro Bartolomucci, Ph.D., Associate Professor in the Department of Integrative Biology and Physiology at the U of MMedical School, and his team, which includes first author Bhavani Sahu, Ph.D., and Yuk Sham, Ph.D., U of M Medical School, discovered that critical mutations in a peptide and a receptor, which are known to be implicated in obesity, diabetes, and hypertensions in rodents, are critical for these biological activities. The findings, published in *Cell Reports*, suggest a new possible therapeutic approach to human disease.

Previous studies identified that a neuropeptide (named TLQP-21) in mice activates a receptor (named C3aR1) to induce the breakdown of fat for the body to produce energy. Bartolomucci and his team started to work in the context of humans and found that the human peptide is not very active in inducing that biological activity, yet the biological pathway is conserved in obesity in humans and mice. They went on to test the rodent peptide with the human receptor and were able to see a biological effect, but found that it wasn't as strong as the rodent peptide with the rodent receptor.

After modeling the peptide/receptor interaction and analyzing the evolutionary history of how different species have evolved over time, they found that the combination of amino acids in the peptide and receptor is unique among the species analyzed and explains the enhanced pharmacological activity in rodent and human cells. This combination is commonly found in a subgroup of rodents, called Murinae, which includes mice, rats and other small rodents commonly used in biomedical research.

"It is tempting to speculate that this cluster of mutations were selected during evolution to favor energy production in small-sized mammals like some rodent species," said Bartolomucci.

To prove this point, the team mimicked what took evolution millions of years to achieve and created a hybrid "murinized" receptor in an in-vitro system. The hybrid receptor has all the amino acids of the human sequence but is mutated by replacing five amino acids of the human sequence with the rodent sequence. The results showed that the mouse peptide (and to a smaller extent, the human peptide) was more potent at the "murinized" human receptor than at the native human receptor, demonstrating that the mutations in the rodent sequence were critical in the evolution of this lipolytic mechanism in rodents.

The rodent peptide could now become an interesting pharmacological target to develop drugs targeting the human receptor. "This could be a starting point for developing drugs that will be based on the rodent sequence of TLQP-21, with the idea that it will be more potent and selective than the endogenous human peptide in activating the C3aR1 receptor and inducing an anti-obesity effect," said Bartolomucci.

More information: Bhavani S. Sahu et al, Peptide/Receptor Co-evolution Explains the Lipolytic Function of the Neuropeptide TLQP-21, *Cell Reports* (2019). DOI: 10.1016/j.celrep.2019.07.101

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