Researchers have uncovered a regulator of body weight that could lead to new treatments for metabolic disorders

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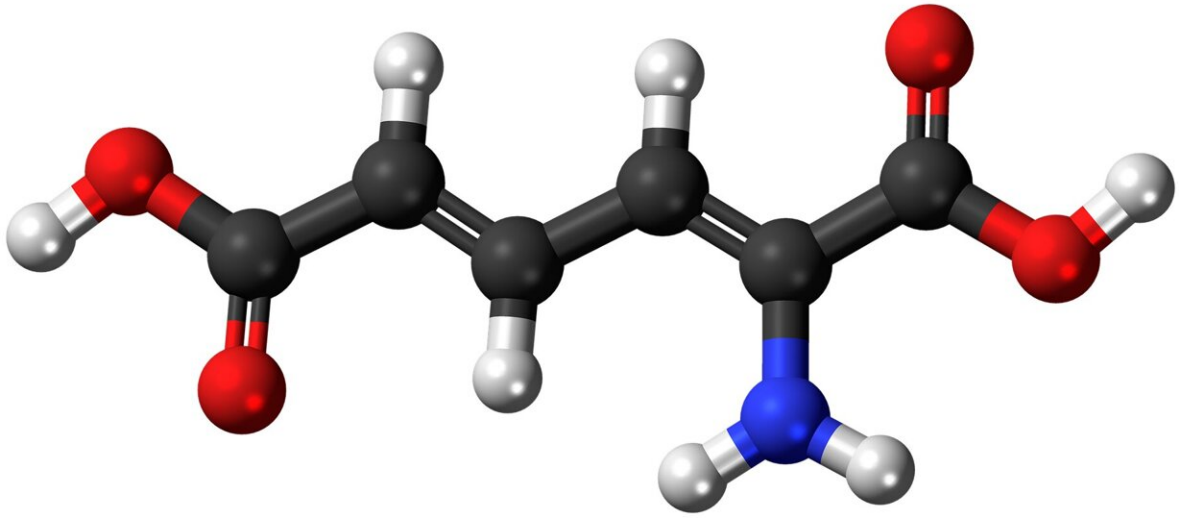

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Yale scientists have discovered that a protein known as augmentor-alpha regulates body weight in mice, an insight that could lead to new treatments for metabolic disorders.

The findings were published April 11 in the *Proceedings of the National Academy of Sciences.*

The research team decided to take a closer look at augmentor-alpha because of its connection to cancer. The protein is known to bind to and activate the anaplastic lymphoma kinase receptor (ALK), a molecule that when mutated, drives a variety of human cancers, including pediatric neuroblastoma, B-cell lymphomas and certain lung cancers.

To better understand this protein and the role it plays in the body, Yale researchers first wanted to pinpoint where it is commonly located. Looking in mice, they found that augmentor-alpha was most strongly expressed in the hypothalamus region of the brain.

In particular, they found it was expressed within cells called agouti-related peptide (AgRP) neurons, which are known to promote hunger.

"AgRP neurons are so important for feeling hunger that without them, you wouldn't eat. You'd die," said Tamas Horvath, the Jean and David W. Wallace Professor of Comparative Medicine and an author of the study. "So when it became clear that augmentor-alpha was dominantly expressed in these neurons, it immediately suggested that augmentor-alpha was involved in metabolism."

The team found further evidence of a link between augmentor-alpha and metabolism when they observed that fasting increased the expression of augmentor-alpha in these neurons.

"Fasting appeared to be a signal to make more of this protein," said Joseph Schlessinger, the William H. Prusoff Professor of Pharmacology, co-director of the Yale Cancer Biology Institute, and senior author of the study.

The researchers then studied mice that lacked the protein altogether. Compared to typical mice, those without augmentor-alpha were thinner, whether they ate a normal or a high-fat diet. They were also more

physically active than typical mice but did not eat significantly more food, which likely contributed to their thinness.

When faced with a lack of food, mice will typically conserve energy and reduce their physical activity, the researchers say. But during fasting, mice without augmentor-alpha were still very active, which suggests the protein is an important signal for energy conservation.

"From what we observed in this study, we think one of augmentor-alpha's roles in the body is to slow down metabolism when there's a lack of food," said Schlessinger. "It's like it is saying, "You don't have food, don't expend so much energy.'"

This link to metabolism suggests inhibiting or enhancing augmentor-alpha's effect could be useful for a number of diseases, researchers said. Drugs that inhibit augmentor-alpha—which certain cancer drugs that target ALK do—could be repurposed for metabolic disorders where excess weight can exacerbate disease. And the enhancement of augmentor-alpha's effect might offer a treatment option for people experiencing harmful weight loss, such as those with anorexia, cachexia, or persistent loss of appetite due to drug side effects or injury.

Recently, Yale researchers, including Schlessinger, uncovered the structure of ALK and how it interacts with augmentor-alpha. Schlessinger said the new findings support and add to what they observed in this earlier research. He compared augmentor-alpha to insulin, which is produced in the pancreas but has effects throughout the body. Conversely, augmentor-alpha is produced in AgRP neurons in the hypothalamus and affects other nearby neurons.

"It acts very locally within the hypothalamus," said Schlessinger.

And that, said the researchers, provides another clue about augmentor-

alpha's role. The hypothalamus controls many essential functions, including reproduction, temperature regulation, and stress response. Augmentor-alpha's effect within the hypothalamus means it could be involved in some of these other processes as well, noted Horvath.

"I think we're just scratching the surface of augmentor-alpha's role," said Schlessinger.

More information: A hypothalamic pathway for Augmentor α–controlled body weight regulation, *Proceedings of the National Academy of Sciences* (2022). doi.org/10.1073/pnas.2200476119

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