Why are you less hungry after vigorous exercise? Credit the ‘anti-hunger molecule’

Scientists are calling it the “anti-hunger” molecule.

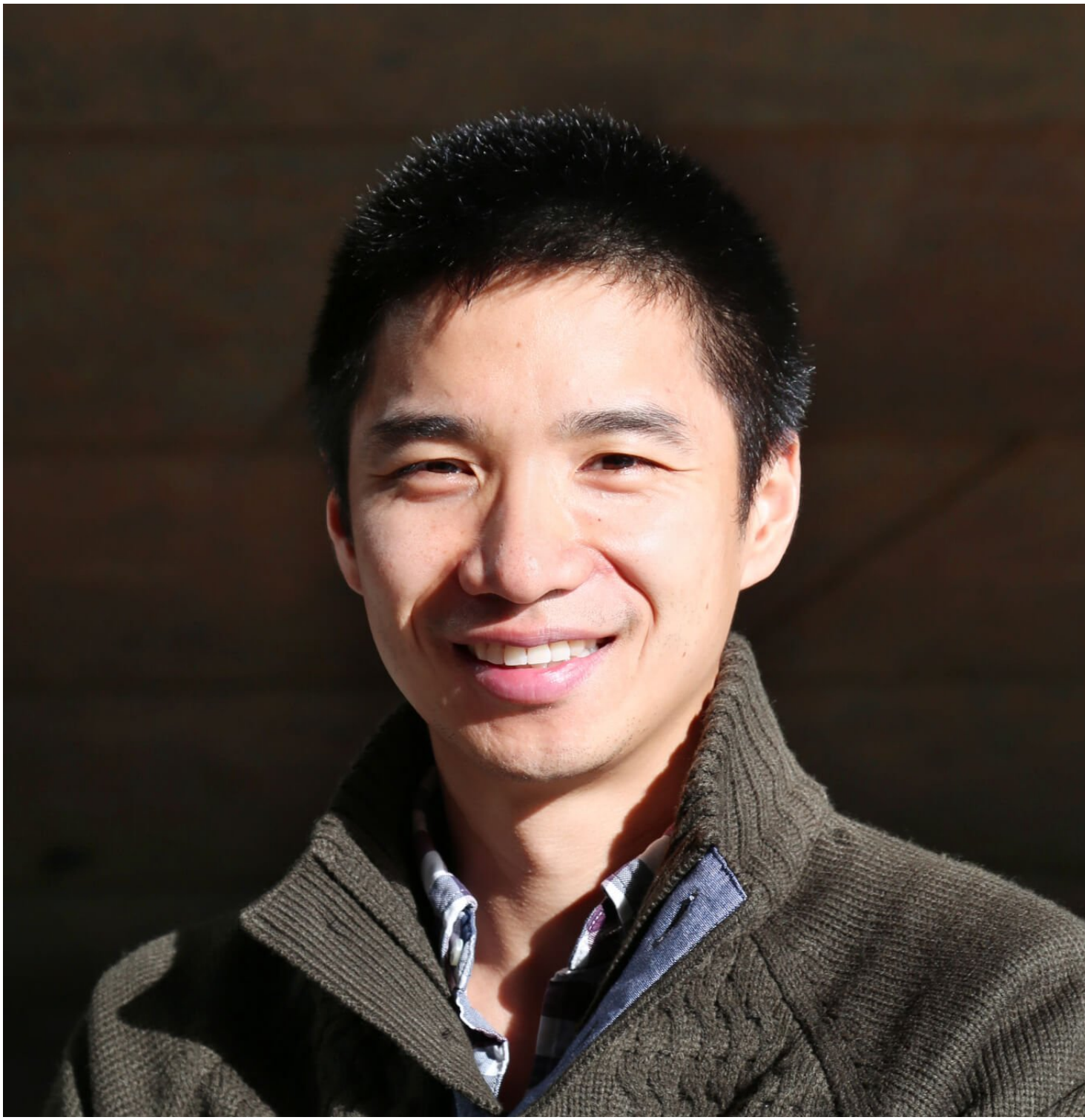
New research shows that a compound induced by intense exercise travels to the brain to stifle appetite. The molecule, identified by researchers at Stanford Medicine, Baylor University and other institutions, helps demonstrate how exercise results in weight loss, and it may hold the key to kickstarting the process in people with metabolic disease.

“We’re all generally aware that exercise is beneficial. It’s good for body weight and glucose control,” said Jonathan Long, PhD, an assistant professor of pathology who led the research. “But we wanted to take a look at that concept in more detail — we wanted to see if we could dissect exercise in terms of molecules and pathways.”

The fruits of Long’s efforts, a molecule known as lac-phe, is a hybrid of two chemical compounds that naturally exist in the human body: lactate and phenylalanine. (When you’ve worked up a good sweat and your stomach feels like it’s about the size of a pea, that’s lac-phe in action.) It’s not just in people — the team also found that the molecule pops up post-exercise in mice and racehorses, suggesting the power of lac-phe may permeate the animal kingdom.

Let’s get to the question everyone wants to know: Does this finding hold promise for that ever-elusive diet pill? There’s potential — but don’t count on it just yet. The discovery does, however, open the door to new explorations of lac-phe-mimicking drugs as a treatment for metabolic diseases such as obesity. But there’s still a lot of work to be done before that could happen, Long said.

A paper describing the finding published in *Nature* on June 16. Long and Yong Xu, professor of pediatrics and nutrition at Baylor College of Medicine, are co-senior authors of the study. Veronica Li, a graduate student at Stanford, and Yang He, PhD, a postdoctoral researcher at Baylor University, are co-lead authors.



Jonathan Z. Long, PhD, of Stanford University. Credit: Stanford University

The skinny on diet and exercise

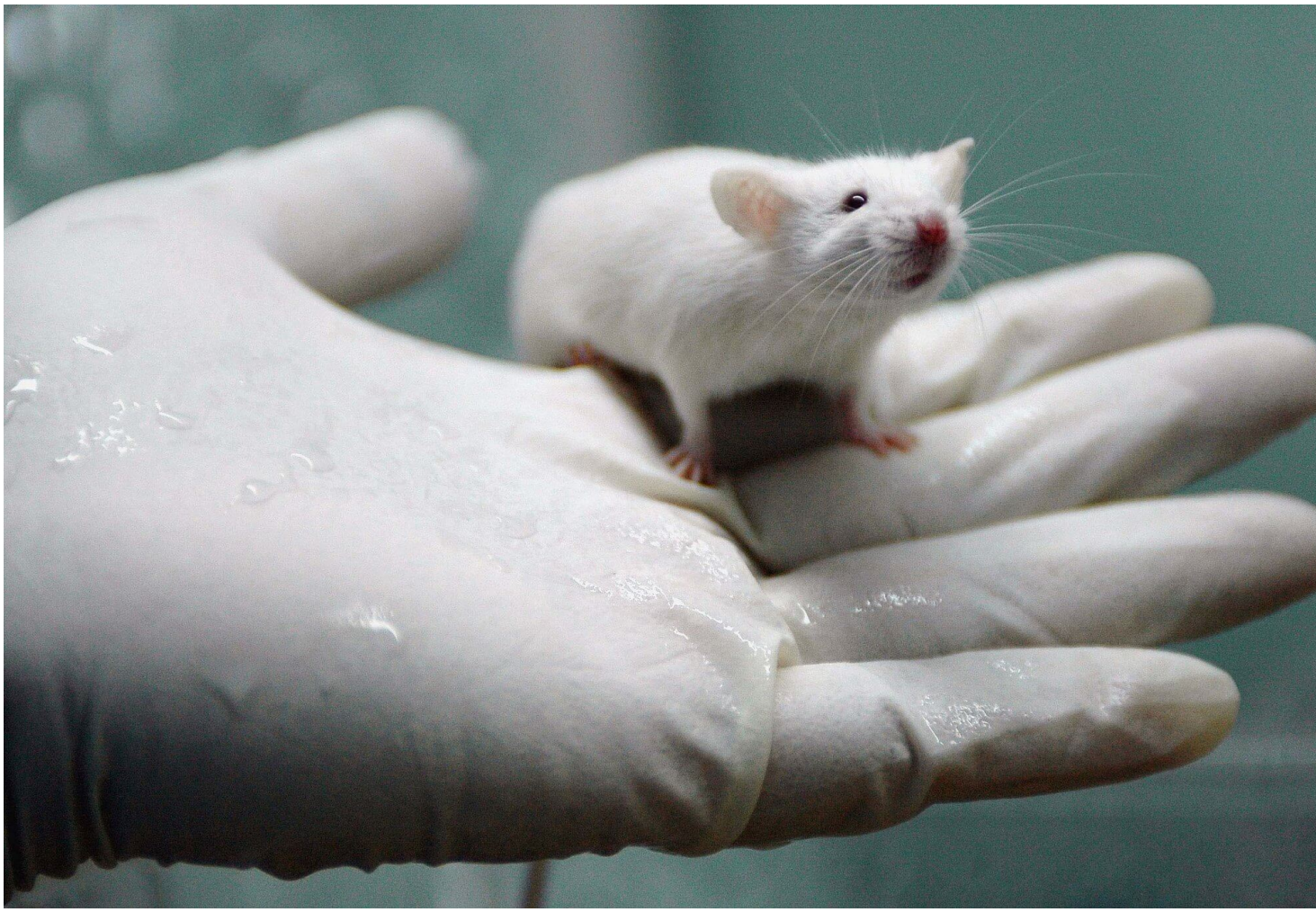
Long and his team set out with a broad objective: to learn something new about the molecular changes that happen in our bodies when we hit the gym. In doing so, they turned to a field of research called metabolomics, which concerns all sorts of molecules that ebb and flow in conjunction with changes in metabolism, particularly during exercise.

Thousands of metabolism-related molecules have been cataloged over the years, and there are likely thousands more not yet identified. “We do, however, know they’re there because we can detect them through our mass spectrometer,” Long said, referring to a machine that can determine the presence of different molecules in tissue or a blood sample based on their weights.

Long and his team decided to use the tool to suss out how small molecules changed during exercise, initially in mice. “We wanted to let the data speak for itself,” Long said. After mice had a brisk jaunt on a treadmill, the researchers looked for signals in their blood that indicated a spike in certain molecules — known as “peaks” in mass spectrometry data. “That way, we just let the biology tell us what’s changing during exercise.”

By comparing mass spectrometry data recorded before and after exercise, the scientists identified a collection of molecules that dipped and spiked, but one stood out. The biggest change came from a molecule measuring 236 on a mass spectrometer.

Long and his team had two new questions: Is this spike only in mice? And is it really caused by exercise, or is it perhaps the result of something else, such as stress?



Credit: New York Times

For answers, they turned to racehorses. Li and Long made a call to Golden Gate Fields, a racing track in the Bay Area, to ask if they could obtain a sample of racehorse blood. Racehorses are frequently tested for enhancement drugs, much like human athletes, a veterinarian at the track told Long. Obtaining a sample of blood from racehorses would be easy. When Long and his team ran the same mass spectrometry experiment, the results again showed a spike of a post-exercise mystery molecule with a mass of 236. “I remember seeing that and thinking ‘OK, there’s something here now,’” Long said.

By chance, Long’s colleague Michael Snyder, PhD, professor and chair of genetics and the Stanford W. Ascherman, MD, FACS Professor in Genetics, MD, had recently published results of a study analyzing the molecular impact of exercise on the human body. It turns out Snyder had also been measuring molecules that shot up during and after exercise. Wouldn’t you know, there was one peak that stood out.

“I emailed the postdoc on the project and said, ‘Listen, we’re looking for this molecule with a mass of 236. Can you see if this is in your data?’” Long said. “A few hours later, I get a response saying, ‘You won’t believe it. But in fact, this molecule was one of our top three hits in our whole dataset.’” Another stroke of

luck: Snyder’s team had just decoded that molecule’s chemical formula, helping the team decipher that it was a combination of lactate and phenylalanine.

It was settled: Lac-phe puts the kabosh on noshing for mice — and likely for racehorses and humans. But how? Lactate, the molecule that creates a burning sensation as you eek out your last rep, increases in our bodies when we exercise. That spike triggers the union of lactate and phenylalanine.

Credit: Aaptive

Hindering the hankering

The study showed that the union of lactate and phenylalanine is catalyzed by a protein called CNDP2, which has high levels of activity in immune and other cells, including skin cells. “That means, when we exercise, many different types of immune cells sense lactate, and then CNDP2 helps create lac-phe,” Long said. Mice lacking CNDP2 were unable to produce lac-phe post-exercise, ate more and packed on more fat than mice with normal CNDP2 activity.

“We estimate that the lac-phe pathway is responsible for about 25% of the anti-obesity effects of

exercise," Long said.

Long and his team also showed that when obese mice were given lac-phe, the mice weren't as hungry and laid off their calorie-dense chow. "We saw their food intake was suppressed by about 30%," Long said. "That led to reduced body weight, reduced fat and improved glucose tolerance, indicative of a reversal of diabetes."

"We thought, 'Wow, all these lines of evidence really suggest that lac-phe is going to the brain to suppress feeding," Long said.

Before we all start looking for lac-phe on drug store shelves, Long cautions that this finding, while exciting, is just the beginning of a series of studies that will dig even deeper into the mechanism of exactly how lac-phe inhibits the hunger signal. That also means zeroing in on which receptors in the brain lac-phe targets. That, he said, is their next step.

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