Far from toxic, lactate rivals glucose as body's major fuel after a carbohydrate meal

May 14 2024

A volunteer is monitored after being given a large dose of glucose to determine how well people switch from fat to carbohydrate metabolism as they age. In the tests at UC Berkeley, subjects had their blood monitored for labeled lactate and glucose, underwent periodic blood sampling, and had their breath monitored for oxygen and carbon dioxide. Credit: Robert Leija, UC Berkeley

As a student competing in track and field at his Parlier high school, Robert Leija was obsessed with how to improve his performance, and in particular, prevent the buildup of lactic acid in his muscles during training. Like many athletes, he blamed it for the performance fatigue and muscle soreness he experienced after intense workouts.

But as a kinesiology student at Fresno State, he was handed an out-of-print textbook that told him he had it all wrong. Lactate wasn't a danger sign that athletes had depleted their body's supply of oxygen, but likely a normal product of the metabolic activity required to fuel the muscles during sustained exercise.

Now, as a graduate student in the University of California, Berkeley, laboratory of the scientist who wrote that textbook, George Brooks, Leija's research is providing a much clearer picture of lactate's role in the body, further refuting the notion that lactate is a sign of oxygen deprivation in the muscles.

In a paper published in *Nature Metabolism*, Leija, Brooks and their colleagues showed conclusively that lactate is produced normally in humans after ingestion of carbohydrates. Lactate rapidly enters the bloodstream, even before glucose shows up. Far from being a toxic byproduct to be eliminated during hard exercise, dietary glucose is converted so rapidly to lactate that it preempts or shares top billing with glucose as the two main carbon-energy carriers in the body.

The results show that the rapid conversion of glucose to lactate, starting initially in the intestines, is a way for the body to deal with a sudden dose of carbohydrates. Lactate, working with insulin, buffers the appearance of dietary glucose in the blood.

"Instead of a big glucose surge, we have a lactate and glucose surge after eating," said Brooks, a UC Berkeley professor of integrative biology.

"And the more of it that is converted into lactate from glucose, the better it is to manage glucose. Lactate is a carbohydrate buffer."

Brooks and his colleagues had earlier shown this to be true during intense exercise. The new study confirms that lactate plays the same role during normal non-exercise activity and resting.

"It's evidence to show that lactate shouldn't be associated with anaerobic metabolism—that is oxygen-limited metabolism. It's just a normal response to consuming carbohydrates or to exercise," Leija said. "In exercise, lactate is utilized as the dominant fuel source. That's why your blood lactate increases as you exercise a little harder. It's not that you're making it as a waste product. It's getting into the blood because it needs to go to tissues that need it to continue their physiological performance."

Glucose tolerance

The study was conducted on 15 healthy, physically active young adults—eight women and seven men—as part of a larger study to determine how well people switch from fat to carbohydrate metabolism as they age. The volunteers were asked to fast overnight (12 hours) to deplete their carbohydrate and glycogen stores so that they were getting energy primarily by breaking down fats into fatty acids and using them to power basic bodily functions.

They then drank 75 grams of glucose, a rapidly absorbed sugar, to stimulate a switchover from fatty acid to carbohydrate metabolism. This is similar to the glucose tolerance test used to diagnose diabetes and is commonly given to pregnant women to screen for gestational diabetes.

Brooks' study differed from previous similar studies in that he and his colleagues, including Leija, closely monitored the volunteers' blood lactate levels over a two-hour period following ingestion of the glucose,

and periodically measured the ratio of oxygen and carbon dioxide in their breath, which indicates the proportion of fatty acids versus carbohydrates being burned.

In order to calculate the amount of lactate that entered the blood compared to glucose, they infused lactate and glucose tracers—lactate labeled with a stable, non-radioactive isotope, carbon-13, and glucose labeled with deuterium—for 90 minutes beforehand to bring the levels of labeled lactate and glucose in the blood to between 1% and 2%.

The dilution of the labeled lactate and glucose by incoming, unlabeled dietary glucose allowed them to establish the kinetics, that is, the appearance, disappearance and clearance of blood lactate and glucose. Most such experiments measure static venous blood concentration, which provides little information about glucose and lactate kinetics.

Sampling of arterialized blood was also key to success of the study, Leija said. That allowed the researchers to see what happened in the gut. Typically, a forearm vein is used to sample blood 30 minutes after a glucose challenge, but that sampling yields muddled results.

The researchers found that the volunteers began converting the dietary glucose into lactate before it even left the intestines. Levels of lactate began rising in arterial blood a mere five minutes after the meal, while glucose, often touted as the energy currency of the body, only showed up in the bloodstream 15 to 30 minutes after glucose ingestion.

"The first carbohydrate after a glucose meal gets into the blood as lactate because that's what intestinal cells do and because most of the glucose is captured by the liver before it is released into the blood for the muscles, where glucose is going to be converted to lactate," Brooks said. "We could see that because of lactate clearance and oxidation and because carbon-13 from the lactate tracer appeared in blood glucose. This shows

that lactate is just a major energy highway for distributing carbohydrate—carbon energy flux."

The lactate shuttle

Brooks has conducted human and animal studies for more than 50 years to investigate the role of lactate in the body, each study providing more evidence that it's not a toxic byproduct of oxygen-limited, anaerobic metabolism, which does not happen in the human body, he said. That assumption, however, has colored the way athletes as well as physicians have looked at lactate. Many physicians still perceive high levels of lactate—often incorrectly called lactic acid—in the blood as a symptom of illness that needs to be fixed with supplemental oxygen or drugs.

"Measuring lactate is one of the major things that sports medicine practitioners do. And now we understand what's happening," Brooks said. "Athletes are producing lactate all the time and clearing it all the time. And when they get to the point where they can't clear it, mostly by oxidation and making it into glucose, we know the person can't persist very long.

"I think this is so revolutionary. But it's really confusing to people. What was bad now is good. All the books are wrong."

The exception is Brooks's textbook, "Exercise Physiology: Human Bioenergetics and Its Applications." Originally written in 1984 with Thomas Fahey, it is now in its fifth edition. Text for the sixth edition is already being uploaded to the publisher.

"When I read through Dr. Brooks's 1984 book, it was a complete mind blow to me, to be honest," Leija said. "I had always associated lactic acid with exercising so hard that I was running out of oxygen and I wasn't putting anything together in terms of physiology. Then it started to make

a lot more sense."

In his book, Brooks coined the term "lactate shuttle" to describe the body's metabolic feedback loop in which lactate is the intermediary sustaining most if not all tissues and organs.

He has shown, for example, that in many tissues, lactate is preferred as a fuel over glucose. During intense activity, the muscle mitochondria burn it preferentially and even shut off glucose and fatty acid fuel use. Brooks used tracers to show that human skeletal muscle, heart muscle and the brain prefer lactate to glucose as fuel and run more strongly on lactate. Lactate also signals fat tissue to stop breaking down fat for fuel.

One gap in these studies was what happens during normal non-exercise activity and resting. The current study fills that gap and supports the idea that when lactate levels in the blood remain high, it is a signal that something is disrupting the lactate shuttle cycle, not that lactate itself is harming the body.

"It's really informative about various medical conditions," Brooks said. "I think what's significant about the current result is that it's just not a muscle thing. It starts with dietary carbohydrate. This was a missing piece in the puzzle."

The recent study is part of Leija's Ph.D. thesis, after which he hopes to conduct further research on the metabolic role of lactate.

"Since before college I would read physiology books trying to improve my training and I would see all these science terms that I kind of ignored back then because I was just looking for 'How can I get faster? How can I run longer?'" Leija said. "But now, wow, it ended up helping me out indirectly. Still to this day, there's so much I think that's left to be uncovered about it."

Other co-authors of the study are graduate students Casey Curl, Jose Arevalo, Adam Osmond and Justin Duong; Melvin Huie, MD, a UC Berkeley graduate affiliated with Brooks's Exercise Physiology Laboratory; and Umesh Masharani, MD, an endocrinologist with UC San Francisco's Diabetes Center.

More information: Robert G. Leija et al, Enteric and systemic postprandial lactate shuttle phases and dietary carbohydrate carbon flow in humans, *Nature Metabolism* (2024). DOI: 10.1038/s42255-024-00993-1

Provided by University of California - Berkeley