Ketostasis: nature's sweet spot

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Credit: Otto Steininger

For followers of popular science news—or of the latest diet craze—the term "intermittent fasting" is decidedly trending. Each new mention of the eating plan brings with it more revelations about the health benefits it could offer.

In the last six months alone, new studies have tied fasting to reduced risk of diabetes, heart disease, and a host of chronic inflammatory diseases. Periodic fasting may also improve symptoms of multiple sclerosis and inflammatory bowel disease. One study found that a 24-hour fast boosts regeneration of intestinal stem cells in aging mice.

But what's behind all these potential benefits of occasionally going without food? Yale research suggests that sugar deprivation gives fasting its many virtues. It may halt or mitigate inflammation that leads to or exacerbates numerous illnesses. And it could be that each of the potential health benefits of eliminating sugar is born of a different mechanism.

Feed a viral infection, starve a bacterial one?

When colleagues Andrew Wang, MD, Ph.D., HS '13, FW '17, and Ruslan Medzhitov, Ph.D., were discussing how they feed their kids when they're sick, they started to wonder what was behind the old adage, "Starve a fever, feed a cold."

"All animals—from worms, to flies, to dogs, to us—do this. When we get acutely infected, we lose our appetite, and people have wondered for a long time why that might be," said Wang, who is an assistant professor of medicine (rheumatology) and of immunology.

The two wanted to find out the potential benefits of fasting during an illness. In their 2016 study, published in *Cell*, when they force-fed an animal that was fighting listeriosis—a bacterial infection—the animal died. On the other hand, feeding an animal battling the flu—a viral infection—helped nurse it back to health.

When the researchers broke the food down into its key components—protein, fat, and sugar—they found that sugar is the active ingredient. Mice that had viral infections needed glucose to adapt to the stress brought on by antiviral inflammation and to prevent stress-induced cell death. In bacterial infections, however, glucose prevented ketogenesis, which was necessary to counteract the oxidative stress of antibacterial inflammation.

Still, Wang said, "As a doctor, I'm hesitant to simply say, 'If you think you have a bacterial infection, starve yourself, and if you think it's viral, don't.' "

And Wang has good reason to hold off doling out that advice. The role of glucose in inflammation is far more complex. New research suggests that glucose deprivation before flu infection may in fact prepare the body to fight it. While glucose after flu infection promotes adaptation to inflammation, a November 2019 study in *Science Immunology* co-authored by Vishwa Deep Dixit, DVM, Ph.D., the Waldemar Von Zedtwitz Professor of Comparative Medicine and professor of immunobiology, suggests mice already in ketogenesis are better equipped to fight the flu once it hits.

In the study, mice that were on the high-fat, low-carbohydrate ketogenic diet when they contracted the flu were more likely to survive the illness than those on a normal high-carb diet. The extremely low-carb diet, the study found, activates a group of T cells in the lungs not previously linked to the immune system's response to influenza. The T cells step up mucus production in airway cells and trap the virus.

While the studies point to opposing roles for glucose in viral inflammation, they also asked different questions.

"Our 2016 study," said Wang, "asks why animals eat less when they have the flu. So, we fed them after they were infected to see what impact that would have. [This new study] asks, 'If an animal is in a ketotic state, how does it affect response to flu infection?' I think what is clear from both studies is that the metabolic state of the organism in an infection—before and during, and probably during recovery—is a critical determinant of the organism's overall outcome in that infection."

Glucose has a role in parasitic infections, too. Wang and Medzhitov

explored this relationship in a 2018 study published in *Proceedings of the National Academy of Sciences* (*PNAS*). When they blocked glycolysis in mice with malaria, the mice didn't go on to develop cerebral malaria.

The glucose deprivation didn't make the mice resistant to malaria. In fact, in both groups, parasite burden, neuroinflammation, blood-brain barrier permeability, and anemia were the same. But, blocking glucose made mice more tolerant of the disease. Or maybe, the study authors suggest, glycolysis inhibition made the parasites themselves less harmful. Either way, fewer microthrombi (tiny blood clots) formed in the brains of those mice, preventing the spread of the infection to the brain.

Burn fat, slow aging

Of course, inflammation isn't only an acute reaction to a new infection. Ongoing inflammation is implicated in nearly all diseases of aging. If modulating glucose can change the course of acute infection, could it also interfere with the lifelong process of aging?

"Most of the cells in the body run primarily on glucose," said Dixit. "So, we wanted to know what happens when glucose is limited." The answer sheds more light on the various health benefits of fasting and low-carb diets like the ketogenic diet.

When the body doesn't have glucose for fuel, it burns fat for energy. This process occurs in fasting, starvation, and in endurance exercise after sugar stores are used up. It also happens on a low-carb diet.

The brain and heart are the biggest consumers of the body's energy. But when the body turns fat into long-chain fatty acids, they can't cross the blood-brain barrier. So, the body converts those into short-chain fatty acids, specifically a ketone metabolite called beta-hydroxybutyrate, for the brain's use.

When the body runs on fat for fuel, Dixit and his team wondered, what happens to immune cell function? Macrophages—mobile white blood cells that gather at infection sites—run on glucose when they are inflamed.

"If macrophages aren't seeing glucose," Dixit added, "but are exposed to alternate fuels instead, how would that affect their activation state?"

What Dixit and his team found was that beta-hydroxybutyrate can block an inflammatory protein complex called the NLRP3 inflammasome. Now, NLRP3 isn't all bad. It plays an important role in triggering inflammation in acute infection. But, Dixit explained, "If it remains chronically activated, it can lead to multiple chronic diseases and it's implicated in the overall process of aging."

When researchers gave beta-hydroxybutyrate to NLRP3-inflamed mice, the ketone metabolite blocked the inflammasome, and the mice did not go on to develop several age-related chronic diseases.

The findings may help explain why popular diets like intermittent fasting and keto bring health benefits beyond weight loss. "Because when one is fasting," Dixit said, "the body has to burn fat, and the metabolites that are increased in this process can potentially reduce inflammation."

Just a spoonful of sugar

This deeper understanding of sugar's role in inflammation could lay the groundwork for both dietary recommendations and medications that regulate glucose in various types of inflammation.

But that doesn't mean sugar is all bad. "The appropriate amount of everything is what we require," said Dixit.

There's not one diet that fits all. "Different types of inflammation require different things," said Wang. "So, you have a lot of moving parts, and figuring out the combination that gives you the best clinical results is not trivial."

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