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Why Do People Become Lactose-Intolerant?

Scientists Turn to DNA in an Attempt to Answer Why Adults Develop Trouble Digesting Milk But Can Eat Ice Cream

By Shirley S. Wang

(See Corrections & Amplifications item below.)

Most of us drank milk every day when we were young without a problem. Then, sometime in our teens or early 20s, we start to feel bloated or have discomfort after consuming a lot of milk, typically two or more glasses at a time.

Scientists have discovered that most people develop some degree of lactose intolerance as they get older. Why we lose this ability to break down lactose, the key sugar found in milk, is a puzzle that researchers have been trying to figure out. The National Institute of Child Health and Human Development, part of the National Institutes of Health, will hold its first conference on the topic next week.

It is unusual for people to lose the ability to digest a nutrient as they age. But most people stop making large quantities of "lactase"—the enzyme that breaks down lactose—after childhood, says Eric Sibley, an associate professor of pediatrics at the Stanford University School of Medicine, who has been studying why people develop lactose intolerance as they get older.

Most people continue to produce some lactase, but at much-diminished levels. After they reach their individual threshold and can no longer break down lactose, it passes intact through the intestine until it reaches the colon, where it is finally fermented by the bacteria that reside there. As the bacteria do their job, they produce gas as a byproduct, which causes discomfort and pain as well as symptoms such as cramping and diarrhea.

Training the Bacteria

Some people, after diagnosing themselves, cut out regular consumption of dairy—which can potentially make symptoms worse when they do consume it. The bacteria in the gut can become less efficient at processing lactose if they aren't continually asked to do it. Conversely, people can train the bacteria to tolerate more dairy if they consume it regularly.

By understanding which genes and proteins are responsible for turning off lactase production, scientists are hoping they can then flip a genetic switch to turn the system back on—but only in the intestine. The hope is one day to be able to "program the intestine to take on the ability to maximally use nutrients," says Dr. Sibley.

This type of complex localized gene therapy isn't likely to be used in run-of-the-mill lactose-intolerant individuals, who can just watch the amount of dairy that they consume or take enzyme supplements. Instead, says Dr. Sibley, it could be used to treat children with serious digestive diseases, such as short bowel syndrome, get the nutrients they need.

Dairy products that have gone through some processing, such as cheese and ice cream, tend to have less lactose because the fermentation process breaks some of it down. But those with an intolerance should keep an eye out for lactose that has been added to products like cookies by reading the food label, says Gilman Grave, acting director of the National Institute of Child Health and Human Development's Center for Research for Mothers and Children.

A separate group of individuals have an allergic reaction to milk that isn't related to lactose. Instead, they are allergic to a protein in cow's milk and tend to have more blood in their stool and abdominal pain, instead of bloating. The allergy typically fades after childhood.

For years, doctors thought that lactose intolerance primarily affected individuals from certain parts of the world, such as Asia and Africa. But newer evidence suggests the opposite is true. Most adults develop lactose intolerance. Only a minority—those descended from herding cultures in northern Europe and parts of Africa—have a mutation that allows them continue to break down lactose into adulthood. The misperception likely developed in part because so many Americans are of northern European descent and have the mutation.

"A lot of people are self-diagnosing themselves with being lactose-intolerant just because they're a member of a certain ethnicity, and they may not be," Dr. Grave says.

Dr. Sibley, who holds a doctorate in biochemistry and also is a pediatric gastroenterologist at Lucile Packard Children's Hospital at Stanford, has spent more than 15 years in the lab investigating genes and proteins that tell the lactase system to shut down production.

To track whether the lactase gene is turned on or off, Dr. Sibley borrowed the firefly's "luciferase" gene, which is responsible for lighting up the firefly's tail. Light is emitted when the gene is turned on.

In the lab, Dr. Sibley and his colleagues take fragments of DNA from regions they think are important to lactase production and graft them into the luciferase gene. They then implant the combination gene into human intestine cells in a dish and allow them to grow. If the DNA fragment indeed starts the lactose production process, it turns the gene on. Thanks to the graft, the turned-on gene emits light, which can be measured.

Using these methods, Dr. Sibley figured out what section of DNA appeared to be responsible for turning the lactase system on and off. In cells from people descended from northern Europeans, a single genetic mutation was associated with the continued ability to tolerate lactose.

They then took cells with those mutations, and in a dish, showed that they increased luceriferase production, which suggests the mutation does change the cell's behavior. These findings were published in 2003 in the journal Human Molecular Genetics.

With the small segment of the African population that is lactose-tolerant, the mutations appear to be slightly different but are located in the same region of the DNA.

Multiple Proteins

Dr. Sibley and his colleagues have also identified several key proteins that must be bound to specific regions of the lactase gene and in the right combinations in order to turn on the gene. One protein they are currently studying, called PDX-1, appears to suppress lactase production in cells in the dish. But when the group generated mice that don't make PDX-1, lactase production was only slightly increased. This suggests that there are multiple proteins working together to suppress lactase and that PDX-1 alone isn't enough to turn the system off completely, says Dr. Sibley.

They also are working to figure out which segment of the DNA sequence tells the lactase gene to produce lactase in certain cells of the intestine but not others, and when the system should be turned off. The ultimate goal of this line of research would be to be able to turn on genes in cells in the intestine that don't naturally produce it, says Dr. Sibley.

Individuals who are worried they are lactose-intolerant can do a self-test by cutting out dairy for two weeks and seeing if their symptoms subside, says Dr. Sibley. There is also a breathalyzer test that measures the amount of hydrogen in the breath, which is a byproduct that bacteria produce if they are breaking down lactose. Most individuals don't need it to be diagnosed with lactose intolerance, according to Dr. Sibley.

For most individuals, lactose intolerance doesn't mean they should permanently cut out all dairy. Studies have shown that people who are lactose intolerant can drink one to two glasses of milk a day without symptoms, says Dr. Grave, who encourages all people without allergies to drink this amount. Many people say their symptoms actually improve when they regularly drink milk, perhaps because the bacteria in the colon break down lactose more efficiently or the number of bacteria build up, he says.

Another reason to drink milk: calcium. If children in particular don't get the amount of calcium they need, their growth and skeletal health may be compromised, says Dr. Grave. A New Zealand study showed that kids on a dairy-free diet get only one-third of their needed daily calcium and had a higher fracture rate, compared with kids who consumed dairy.

It is certainly possible to get calcium from other foods, but people would have to eat vast amounts of it in order to get the same amount found in dairy, says Dr. Grave. For instance, you would have to eat many servings of spinach in order to absorb the same amount of calcium you would get in one cup of milk.

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Corrections & Amplifications:

Eric Sibleyis an associate professor of pediatrics at the Stanford University School of Medicine. Tuesday's In the Lab column on lactose intolerance incorrectly identified him as an assistant professor.