Working out how the ability to digest milk spread

Humans have been drinking milk for thousands of years, but it seems that they were doing so long before the ability to digest it became prevalent. Then, around 2,000 years ago, this ability became common in Europe, presenting a mystery to researchers — why then? Now, by analysing health data, ancient DNA and fats residues from thousands of ancient pots, scientists have worked out what caused this trait to suddenly spread throughout Europe.

Research Article: *Evershed et al.*

News and Views: *The mystery of early milk consumption in Europe*

TRANSCRIPT
Listen to the latest science news, with Benjamin Thompson and Nick Petrić Howe.
Host: Nick Petrić Howe

Welcome back to the *Nature Podcast*. This week: how drinking milk didn't necessarily lead to our ability to digest it.

Host: Benjamin Thompson

And assessing the potential for therapeutic ketamine to become addictive. I'm Benjamin Thompson.

Host: Nick Petrić Howe

And I’m Nick Petrić Howe.

[Jingle]

Host: Nick Petrić Howe

First up on the show, there’s been a long debate in archaeology about when humans evolved the trait to digest lactose – one of the key ingredients in milk. But now, a paper in *Nature* has been digging through fat remains in thousands of ancient pots to try and work it out. Reporter Alex Lathbridge is here with more.

Interviewer: Alex Lathbridge

What did you have for breakfast this morning? If you’re anything like me, it was cereal, or maybe yoghurt, or maybe, if you’re feeling fancy, a bit of cheese on toast. So, a very milky morning. But for many people, this wouldn’t be such a pleasant start to the day. If you’re lactose intolerant, it means you don’t have the enzyme lactase, and so can’t naturally break down one of the key ingredients of milk – lactose – into sugars that you can then digest. Instead, bacteria do the job, and that means flatulence, diarrhoea and bloating. Basically, your breakfast is bad vibes. And for tens of thousands of years, that was the norm. But somewhere along the line, some humans developed a mutation in a single gene that meant that the lactase that’s present when you’re a baby persisted into adulthood. But the question is, why?

Interviewee: Mark Thomas

We already knew that this trait – lactase persistence – had been under extremely strong natural selection, stronger than any other trait that's determined by a single gene over the last 10,000 years, at least in Europeans but also in many African, Middle Eastern and southern Asian populations. So, we know that's the case. That's the background. So, now, we want to explain that.

Interviewer: Alex Lathbridge

That is Mark Thomas, evolutionary geneticist as University College London. He's been part of a team of researchers who've been trying to explain why, over the last 10,000 years, people in Europe have developed that important mutation that allowed them to consume lactose went into adulthood. So, the first step in examining this mysterious milky mutation is understanding when people in the past started to raise cattle and consume dairy.

Interviewee: Mark Thomas

So, cattle were domesticated in the Middle East, probably around 10,5000 years ago. So, when those farmers moved into Europe, they brought their domestic animals with them. And for a long time, many people thought that people kept those animals but they didn't milk them and milk came later. And this is where my colleague in Bristol, Richard Evershed, who's the lead author on the study, comes in. So, he's developed and his team have developed these amazing

techniques where they can get organic residues out of pots, and then they can tell the difference between fats that come from milk, or fats that come from carcass or fats that come from certain animals. And they've amassed quite a lot of data on milk use over time, over the last 9,000 years in Europe. What they showed was that it was right there at the start, that it stays consistently. It does change in amount, so people seem to use less milk or more milk at one time to the other. But basically, it's there, and it's there from the beginning. So, now, we've got this picture of changing milk use through time and in space.

Interviewer: Alex Lathbridge

So, alongside this picture mapping out ancient milk consumption, they took available ancient DNA samples from across Eurasia. Using a statistical model, they asked the simplest question: does higher dairy consumption link to a higher presence of lactase persistence? Or in even simpler terms: does more milk mean more lactase? The answer? No, not really. And that makes sense. Because it's not as though farting, bloating and other side effects of drinking milk are in any way life threatening, or maybe that's not always the case.

Interviewee: Mark Thomas

In famine conditions, diarrhoea can turn from an inconvenient to a fatal condition. And under famine conditions, those are the conditions under which they will be more likely to drink the fresh, high-lactose milk. And so, they are giving themselves diarrhoea at the time when they really

shouldn't be. And this is where another Bristol colleague, George Davey Smith, comes in. So, George has this very nice idea that you wouldn't get lots of lactase non-persistent people dying unless they were exposed to pathogens. So, when they're exposed to pathogens, because of gut disturbances and the fact that drinking milk is going to give them, to some degree, diarrhoea, that that's the time when natural selection would have been very strong. So, we have these two related ideas that famine and disease are actually the real things that are driving this turbocharged natural selection on lactase persistence.

Interviewer: Alex Lathbridge

But how do you link this to things that happened thousands of years ago? Because it's not like you can go into the deep, deep past and use census data to see exactly when a famine happened. Well, Mark and his colleagues came up with a way to figure it out.

Interviewee: Mark Thomas

Now, fortunately, we've got something that approximates those from the archaeological record. If we look at radiocarbon dates, we can get an idea of how clustered people are. The more clustered people are in terms of living space, the more likely they are to be exposed to infectious diseases. And also, we can get an idea of when populations are going up and down. And when populations stop going up and start going down rapidly, that usually indicates some sort of famine exposure or something like that. So, now, we can put these other predictors, if you like, of lactase

evolution into our model, into our new statistical approach, and we found that they do explain it. They actually explain it loads better than milk use and loads better than just assuming that the selection was constant through time. So, it appears that selection was stronger under famine conditions, and it appears that selection was stronger when populations were more clustered, and from that we infer more exposed to pathogens.

Interviewer: Alex Lathbridge

Now, this study focused on Europe, but could this pattern of lactase persistence being linked with famine and disease be found in other populations that drink milk? I asked Mark.

Interviewee: Mark Thomas

That's a really good question. Well, the correct answer is: we don't know. But those issues of famine and disease exposure are fairly universal in human prehistory wherever you go. So, I wouldn't find it surprising if, one day, we found that that was the case in Africa and the Middle East and southern Asia as well. There is some milk use data, but we need more ancient DNA data on the frequency of those lactase persistent genetic variants. And one of the factors that strongly influences the survival of DNA in old bones is temperature. One of the advantages of studying Eurasian populations, particularly northern Eurasian populations, is that they tend to be colder environments and so DNA tends to survive better. But there is ancient DNA data from many African populations, and one day we'll have enough and

then we'll be able to look at this question in those populations as well.

Host: Nick Petrić Howe

That was Mark Thomas from University College London here in the UK. For more on that story, check out the paper in the show notes.

Host: Benjamin Thompson

Later in the podcast, we'll be hearing how researchers have been assessing the risks that therapeutic ketamine use could lead to addiction. Right now, though, it's time for the Research Highlights with Dan Fox.

[Jingle]

Dan Fox

Insects might be genetic kleptomaniacs, snagging more than 1,400 genes from bacteria, fungi, plants and viruses, according to an analysis of 218 insect genomes. Pilfered genes have been sporadically seen in insects before, but now researchers have looked for signs of this in 218 genomes and found nearly 750 acts of thievery, with these genes coming from outside the animal kingdom. The team found the most prolific evidence of gene grabbing in the order *Lepidoptera*, which includes butterflies and moths. These genomes contained an average of 16 transferred genes. The stolen genes help insects to neutralise toxins

and adapt to extreme environments. They're even involved in courting behaviour, with one prevalent gene transferred from a bacterium into a shared ancestor of almost all moths and butterflies. Steal some time to read that research over at *Cell*.

[Jingle]

Dan Fox

A dormant black hole spotted outside our Galaxy has provided a glimpse of the processes that accompany their formation. A stellar-mass black hole is born when a massive star collapses under its own gravity. Billions of these objects are thought to reside in the Milky Way and its neighbouring galaxies, but only a few are known. Researchers have discovered one such black hole in a nearby galaxy called the Large Magellanic Cloud. The object is at least nine times the mass of the sun and orbits an even bigger hot, blue star. Unlike previously reported black holes outside the Milky Way, this one is dormant, meaning it doesn't emit high levels of X-ray radiation. The authors found that this black hole seems to have formed without a powerful explosion or supernova, adding credence to the idea that a massive star can collapse directly to produce a stellar-mass black hole. They say that this finding has implications for the detection of gravitational waves resulting from merging black holes. You can spot that research in full in *Nature Astronomy*.

[Jingle]

Interviewer: Benjamin Thompson

Ketamine is a drug with a varied history. It was developed in the 1960s as an anaesthetic, and it is also used as a recreational club drug. But in the past couple of decades, there is a third use that has become apparent that has gotten researchers rather excited. Ketamine appears to work very effectively as a fast-acting antidepressant. However, there have been concerns about the potential risks of addiction relating to this therapeutic use. To understand more about this potential, a team of researchers have a paper out in *Nature*, in which they've been looking in mice to see whether ketamine causes the behavioural and neuronal changes characteristic of addictive substances. I spoke to one of the authors of the work, Christian Lüscher from the University of Geneva, who gave me a sense of why there are concerns that ketamine might have addiction potential.

Interviewee: Christian Lüscher

Well, precisely because it's, on one hand, a medically prescribed drug, and on the other hand, a recreationally abused drug, people know that there might be a risk of inducing addiction. So, that definitely is something that is hotly debated in the field, and there's precedent from other drugs. I mean, probably the most stringent example are the opiates that are typically used to treat pain. And we know they are addictive, and it has become a major public health issue, especially in the United States. So, prescribing drugs that have a potential of inducing addiction needs to be done very carefully.

Interviewer: Benjamin Thompson

And what was previous work showing about the potential addictiveness of ketamine then?

Interviewee: Christian Lüscher

So, previous work was showing that there are some anecdotal reports of people who do start to abuse ketamine. But what was not known is what exactly its pharmacological action is on those circuits and centres that typically are activated by addictive drugs. So, in this new paper, we basically put ketamine to the test, looking into mouse brains, both on the neural as well as on the behavioural level, for its addiction liability.

Interviewer: Benjamin Thompson

And you start with the behavioural aspects then and looking at what happens when mice are given ketamine and comparing it to cocaine, which, of course, is a very addictive drug.

Interviewee: Christian Lüscher

Absolutely, so the first thing we do is to see whether an animal will self-administer a drug. And so, we know that for addictive drugs, this is one of the initial elements. So, if an animal can press a lever, to inject, for example, cocaine, they will do so readily. So, we started with that and asked, is ketamine leading to that self-administration? Is it reinforcing

that behaviour? And it actually did, so at this very early step, there are some commonalities between addictive drugs and ketamine.

Interviewer: Benjamin Thompson

What is the difference between reinforcement and addiction then, Christian?

Interviewee: Christian Lüscher

Well, reinforcement means that a certain behaviour is repeated again and again, if the animal receives the drug reward. Addiction, on the other hand, is a much later step when this behaviour actually continues despite negative consequences. So, we define drug addiction as the compulsive use of a substance despite major negative consequences.

Interviewer: Benjamin Thompson

So, in the short term then, you've looked at these mice and they will readily take ketamine if it's available. But then you've looked inside their brains to see what's happening, and it seems that key to this is dopamine.

Interviewee: Christian Lüscher

Yeah, so, absolutely. So, the next step, once we have this behavioural observation that it is reinforcing, we ask is it

reinforcing the same way that we usually observe it with addictive drugs. That is, is the dopamine – a chemical in the brain – increased in a very specific part of the brain that we call the mesolimbic system? And we saw that this is indeed the case for ketamine. We already saw, however, that how quickly that dopamine then returns to baseline is much faster for ketamine compared to, for example, cocaine.

Interviewer: Benjamin Thompson

And so, what's causing this difference in the mice who are given ketamine?

Interviewee: Christian Lüscher

So, what it turns out is that it is not the cells that produce the dopamine that is the initial target of the ketamine, but it is inhibitory neurons that are upstream of these dopamine neurons. The initial molecular target is a receptor called the NMDA receptor. So, when ketamine gets into the brain, it blocks that receptor. And as a result of that, the inhibitory neurons onto dopamine neurons become less active. And normally, these inhibitory neurons sort of set the brake to the dopamine neurons. And what ketamine does, it shuts down these inhibitory neurons, and that is leading them to a disinhibition. So, it's a cellularly distinct mechanism through which ketamine increases dopamine compared to cocaine.

Interviewer: Benjamin Thompson

So, when the drug is administered then, the drug actually takes the brakes off dopamine production for a short amount of time, so you get this big spike, but then the brakes are put back on and the level drops down.

Interviewee: Christian Lüscher

Yeah, absolutely.

Interviewer: Benjamin Thompson

So, if that's what's happening in the short term in the brains of the mice, what happens in the longer term and how does that relate to addiction?

Interviewee: Christian Lüscher

So, the longer-term effects are then mediated by the dopamine that is increased, and it consists of changing communication between nerve cells. We call this synaptic plasticity. And if that synaptic plasticity occurs at specific synapses, the animal will start to change its behaviour. And with time, that may evolve all the way to compulsion – that is the use of the drug despite the negative consequences. So, with ketamine, what we see is that this increase of dopamine is quick and, in most instances, not sufficient to trigger this cascade of changes in synaptic communication. And even if you force ketamine to induce longer-lasting dopamine transience by giving ketamine again and again and again, it still doesn't do it because the receptor that is blocked by ketamine – the NMDA receptor – is necessary

for these changes in synaptic plasticity. And if that cannot occur, the animal will not progress to the behavioural changes that are typically seen with addictive drugs and will not become compulsive.

Interviewer: Benjamin Thompson

And was this a surprise to you then to see such a difference compared to an addictive drug like cocaine?

Interviewee: Christian Lüscher

I mean, what is certainly a surprise to us is that we have this unique constellation of an increase of dopamine in the beginning, yet no subsequent changes in synaptic communication. That is, for us, the first time we see this with a pharmacological substance, so that is quite unique for ketamine.

Interviewer: Benjamin Thompson

And what does this mean overall then?

Interviewee: Christian Lüscher

So, overall, it means that the addiction liability of ketamine is likely to be very low. And I think that is an important element to keep in mind in the discussion when it comes to access to care. Who should receive ketamine to treat depression? So, there are discussions currently going on that people who

actually already have a known vulnerability for addiction, that they should not be treated with ketamine. And so, in that discussion, to sort of have a rational base on the neural mechanisms that are engaged in ketamine can be extremely helpful.

Interviewer: Benjamin Thompson

But of course, this work is in mice, and we know that addiction is very, very complicated. And in some cases, many different parts of the brain are involved. So, you found this one for ketamine. Just because it appears, in this instance, its addiction liability is low, it doesn't mean that it is not addictive.

Interviewee: Christian Lüscher

Absolutely, so we have to be careful and we have to acknowledge that mouse models of addiction do not reflect the entire complexity of the human disease. What we can do is we can observe some of the core components of the disease. But obviously, we still remain in an animal model, and it needs to be tested now in clinics whether this holds true.

Interviewer: Benjamin Thompson

And finally then, what is your hope, I guess, overall? If this work does prove to translate into humans, what can it mean?

Interviewee: Christian Lüscher

Well, so, our hope is that our conclusions in the mouse model is confirmed in the humans. That is that ketamine is a relatively safe drug and should not be withheld from people who actually need it to treat their depression.

Interviewer: Benjamin Thompson

That was Christian Lüscher from the University of Geneva in Switzerland. For more on this work, look out for a link to the paper in the show notes.

Host: Benjamin Thompson

Finally on the show, it's time for the briefing Chat, where we discuss a couple of articles that have been featured in the *Nature Briefing*. And joining me to do so this week is Flora Graham, who looks after all things Briefing. Flora, how are you doing today?

Flora Graham

Really well, thanks so much for having me.

Host: Benjamin Thompson

Not at all, great to have you on the show. So, a couple of stories to talk about today. The first one, we're going to head over to Australia. What's been going on there?

Flora Graham

Well, every five years, a report comes out in Australia about how its ecology is doing, how its environmental systems are doing. And I'm very sorry to say that this report has got some very bad news.

Host: Benjamin Thompson

Yes, there's been a lot going on there recently. We've covered a bunch of things on the show. There's been droughts, incredible bushfires. I think that like a billion animals may have perished, which is very, very sad. We've covered the floods and coral bleaching and all sorts going on. It hasn't been good news.

Flora Graham

That’s right, and I think Australia has always been under pressure since colonialism began from invasive species as well. And combining that with more land being taken for agriculture, what we're seeing is that the state of Australia's environment, well, they characterised it as poor and deteriorating. So, we've got issues where the country now has more non-native plant species than native species. It has more mammal species that have gone extinct than on any other continent. And the report numbered 19 of Australia's ecosystems that are on the verge of collapse.

Host: Benjamin Thompson

Well, there's a lot in there, Flora, and you're right, it doesn't sound like good news at all. You said this has all been collated in one report. How does this compare to what's come before?

Flora Graham

I mean, I think that, as we have all seen, it feels like many of these factors are kind of building perhaps even faster than we thought that they might. But I should add that there are glimmers of hope in the report. The authors, for the first time, have included a section about Indigenous stewardship and Indigenous perspectives which they say, along with hard work from many people in Australia, offer examples of how there are pockets of improvement. There are ways in which people and the environment can work together successfully. And what they really emphasised from this new section is that human wellbeing is intrinsically linked with environmental wellbeing.

Host: Benjamin Thompson

And what are some of the examples of these Indigenous practices then that have been highlighted?

Flora Graham

I think a key one that authors point to, especially considering the unbelievably destructive wildfires that have been seen in Australia, is traditional fire management, and that seems to be an area also that's getting a lot of attention in the United

States, where you had traditional burning practices – the idea that you might burn purposely certain areas. Now, it's not an uncontroversial approach. But the authors of this report certainly do point to it as being vital for land management.

Host: Benjamin Thompson

So, some glimmers of hope, as you say then, Flora, but vastly outweighed, dare I say, by the negative aspects of this report. What are researchers saying about it all?

Flora Graham

Absolutely. Well, the authors did a very clear, I thought, job of explaining the report on *The Conversation* website. And they really lay out how it assesses every aspect of the environment, rivers, oceans, air, ice, land, city, and how it does go a little bit further to talk about people's wellbeing as well as those people who are successfully finding these little pockets of hope, within the absolutely, as you say, very widespread and general issues.

Host: Benjamin Thompson

And what are researchers saying about the likelihood of this report leading to action from government officials and what have you in Australia?

Flora Graham

I mean, I think the Australian political landscape has long been a place where researchers, conservationists and people concerned for the environment have not seen the level of adaptation and the level of urgency that they would have liked to have seen from the government. And that is one area that, again, the report authors point out that environmental management is not well connected on the continent. So, things are maybe done in a more piecemeal way when facing huge interconnected and, in fact, global challenges. It's just not good enough. Now, the government has recently changed in Australia. And I think, from what I understand from our coverage of the Australian political landscape, climate change and the environment are key, key issues for Australian voters, so one can only hope that the pressure from the voters will have a positive toll.

Host: Benjamin Thompson

Well, certainly a sobering story, Flora. It's an Australian-centric report but I guess it definitely has echoes and important information for the whole world. But let's move on to our second story today that we're going to talk about, and it's about rice.

Flora Graham

Yeah, rice is a food that feeds the world and making it increase its yield could make it do even more. And so, it's quite interesting to see that scientists have managed to tweak some genes in rice in order to increase its yield by 40%.

Host: Benjamin Thompson

Yeah, I've had a bit of a read of this one actually ahead of time, and this is a story that was in *Science*, and it seems, from what I've read, that working out ways to increase yield has been quite difficult in terms of genetics because researchers have been looking for that kind of one gene that makes the plant twice as big or whatever it may be, and that hasn't necessarily been too fruitful. So, in this case, they've been looking at genes that control genes – these things that are called regulatory genes – that I guess are kind of a switch that switches on maybe other things, so maybe you could find one gene that would switch on a bunch of things, like make a plant grow bigger, or make it photosynthesise more, or make its roots more efficient at absorbing nutrients from the soil, right?

Flora Graham

Yeah, they seem to have done the job. They did find one gene where, when they inserted an extra copy, now this was in a variety of rice that's used in the laboratory, the rice had better photosynthesis, it produced more grains. And when they knocked out the gene, they did find that those plants grew less well than control plants.

Host: Benjamin Thompson

But I think what's neat as well is that it's not just necessarily like research plants. They've actually brought this out into the field and, as you say, increase the number.

Flora Graham

Yeah, I think that that's the big news here is that, from what I understand, it's been a big challenge to make changes that seem to be effective in the lab be effective in the much more complex environment of the field. And the researchers did find that in a very commonly used by farmers variety of rice, they still saw an improvement. Now, not necessarily the same level of improvement to yield as they saw in the lab, but still a big improvement. And another interesting factor is that they made the same kind of change in wheat, and they found that seemed to also have a boosting effect. So, this could be a finding that has much broader implications.

Host: Benjamin Thompson

Yeah, because increasing yields is really, really important as the global population gets bigger.

Flora Graham

Yeah, I mean, the kind of unspoken question here is: to what extent will markets accept genetically modified rice? But in this case, the researchers do say that they could possibly achieve the same improvements by editing the plant's own genes, rather than inserting a gene, which means that it wouldn't be considered genetically modified under a lot of regulatory regimes and maybe a bit more palatable to some consumers.

Host: Benjamin Thompson

Well, let's leave it there for today's Briefing chat then. And for listeners who want more stories like this delivered directly to their inbox, what do they have to do to sign up for the *Nature Briefing*?

Flora Graham

Well, if you would like to read more of this great science journalism, both from *Nature* and from other publications, please do sign up for the *Nature Briefing* at nature.com/briefing.

Host: Benjamin Thompson

Well, thank you very much for joining me today, Flora, and we'll put links to today's stories in the show notes as well.

Host: Nick Petrić Howe

That's all for this week. As always, you can reach out to us on Twitter – we're @NaturePodcast. Or you can send us an email to podcast@nature.com. I'm Nick Petrić Howe.

Host: Benjamin Thompson

And I'm Benjamin Thompson. See you next time.