Researchers uncover mechanism that may explain why some people can't stop binging on unhealthy foods

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People overeat and become overweight for a variety of reasons. The fact that flavorful high-calorie food is often available nearly everywhere at

any time doesn't help. Buck researchers have determined for the first time why certain chemicals in cooked or processed foods, called advanced glycation end products, or AGEs, increase hunger and test our willpower or ability to make healthy choices when it comes to food.

"This research, done in tiny nematode worms, has immense implications for human dietary choices and the propensity to overeat certain foods," said Buck professor Pankaj Kapahi, Ph.D., the senior author of the study. "Processed modern diets enriched with AGEs are tempting to eat but we know very little about their long-term consequences on our health." The work is published in *eLife*.

"Humans evolved certain mechanisms that encourage us to eat as much food as possible during times of plenty. We store the excess calories as fat that we use to survive times of fasting," explained Muniesh Muthaiyan Shanmugam, Ph.D., a postdoctoral research fellow in the Kapahi laboratory, and the lead author of the study. "Natural selection favored genes that makes us preferentially consume flavorful food, especially those with higher sugar content. But what is the mechanism that makes it so hard to say 'no' to them?"

AGEs are metabolic by-products that occur when a sugar combines with part of a protein, lipid or nucleic acid. They occur naturally when we metabolize sugars in a cell, but AGEs are also created during baking, frying and grilling, and are in many processed foods. "The brown color that occurs during cooking, which makes food look and smell delicious is a result of AGEs," said Shanmugam. "Basically, we are finding that AGEs make food more appetizing and harder to resist."

The "browning" reaction that occurs when sugar and protein interact with heat, beloved among chefs, is called the Maillard reaction. It results in the formation of hundreds to thousands of enticing AGEs.

But while the Maillard reaction's claim to fame is its ability to make foods taste delicious, the resulting chemicals wreak all kinds of havoc in the body. They cause inflammation and oxidative damage, contributing to the development of blood vessel stiffening, hypertension, kidney disease, cancer, and neurological problems.

The accumulation of these metabolic by-products in several organs is probably one of the major drivers of aging of various organs and the organism as a whole, said Kapahi, whose lab focuses on how nutrients influence health and disease.

"Once advanced glycation products are formed, they cannot be detoxified," Shanmugam said. Just as toasted white bread becomes brown, the process can't be reversed to make the bread white again. "Similarly, there is no way to reverse the AGEs," adding that the body's ability to clear AGEs declines with age, providing another link to age-related disease.

Even the tiny worms in the Kapahi lab could not escape the allure and damages caused by AGEs. Researchers observed that these chemicals, in addition to causing disease and decreasing longevity, also increased the worms' appetite for more of the same. The researchers wanted to know the mechanism by which AGEs spur preferential overeating.

To uncover the biochemical signaling pathway responsible for overeating in normal healthy worms, the researchers purified some well-studied AGEs and found two of them that increased eating. They further explored one of the compounds to find out the signaling mechanism. They showed that a particular mutation (called glod-4) increased food intake, mediated by a particular AGE (called MG-H1). Further analysis revealed a tyramine-dependent pathway was responsible.

Their work is the first to identify the signaling pathway mediated by

specific AGEs molecules to enhance feeding and neurodegeneration. They also found that mutant worms that have no way to process even naturally occurring AGEs have approximately 25–30% shorter lifespans. The work is being extended into mice where researchers will look at the connection between AGEs and fat metabolism.

"Understanding this signaling pathway may help us to understand overeating due to modern AGEs-rich diets," said Kapahi. "Our study emphasizes that AGEs accumulation is involved in diseases, including obesity and neurodegeneration. We think that overall, limiting AGEs accumulation is relevant to the global increase in obesity and other age-associated diseases."

The message that Shanmugam takes from his work is profound. "We are not controlling our food intake, instead it is the food that is attempting to control us," he said.

As a result of this and previous research from the lab, Shanmugam and Kapahi have changed the way they view their own diets. They both practice intermittent fasting, which gives the body a chance to use fat instead of sugars. There are simple things that anyone can do to reduce the burden of AGEs in their bodies, said Kapahi, including eating whole grains (the fiber helps maintain stable glucose levels), cooking with wet heat rather than dry (i.e., steaming vs. frying or grilling), and adding acid when cooking foods which slows the reaction that leads to the formation of AGEs.

"We are naturally attracted to delicious food, but we could be more mindful that we do have the ability to make healthy choices when we eat," said Shanmugam.

More information: Muniesh Muthaiyan Shanmugam et al, Methylglyoxal-derived hydroimidazolone, MG-H1, increases food intake

by altering tyramine signaling via the GATA transcription factor ELT-3 in Caenorhabditis elegans, *eLife* (2023). DOI: 10.7554/eLife.82446

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