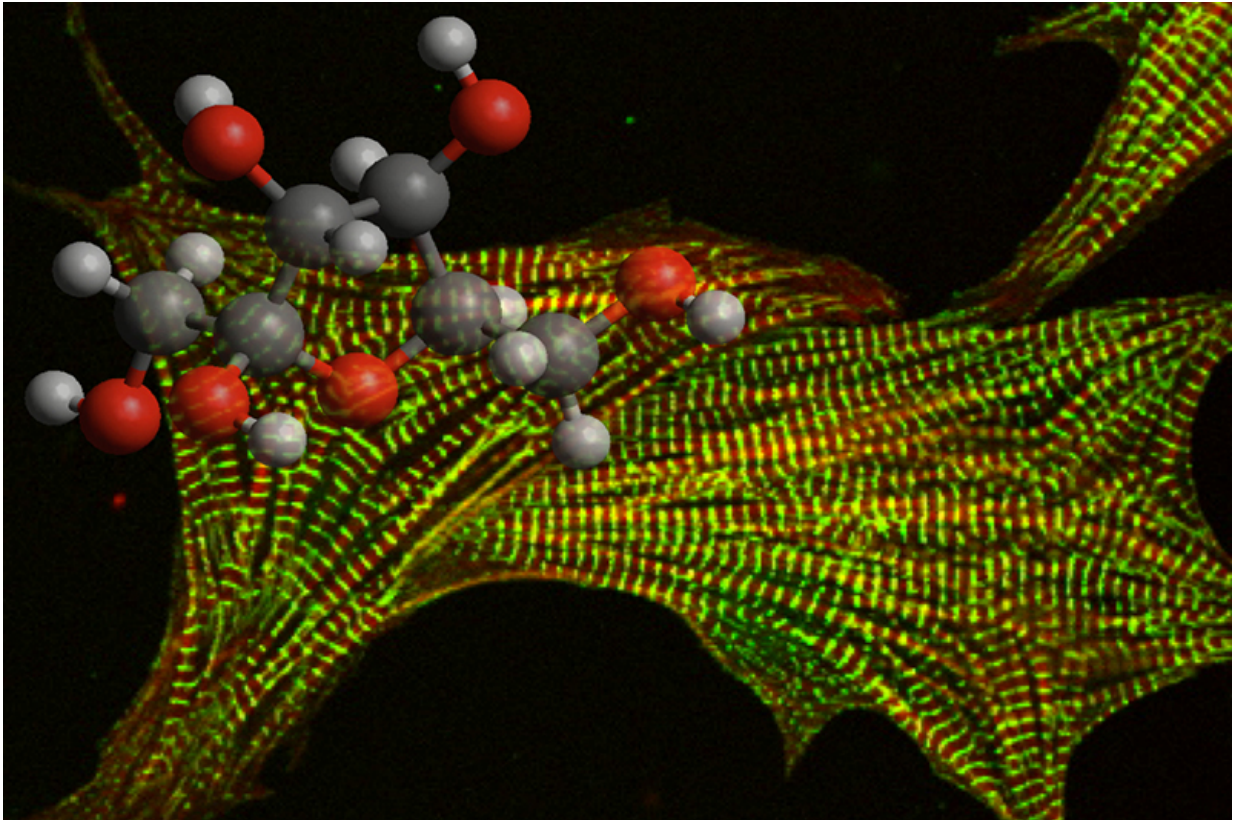


# Fructose powers a vicious circle

June 17 2015

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High consumption of fructose can lead to uncontrolled growth of cardiomyocytes and heart attack. Credit: ETH Zurich/Peter Mirtschnik and Tatiana Simka

ETH researchers have found a hitherto unknown molecular mechanism that is driven by fructose and can lead to cardiac enlargement and heart failure.

'Walk through any supermarket and take a look at the labels on food products, and you'll see that many of them contain [fructose](#), often in the form of sucrose (table sugar)'—that's how Wilhelm Krek, professor for cell biology at ETH Zurich's Institute for Molecular Health Sciences, summarises the problem with today's nutrition. Prepared foods and soft drinks in particular, but even purportedly healthy fruit juices contain fructose as an artificial additive—often in high quantities. In recent decades fructose spread throughout the food market, due to a reputation as being less harmful than glucose. In contrast to glucose, fructose barely increases [blood glucose levels](#) and insulin secretion. This avoids frequently recurring insulin spikes after any glucose consumption, which are judged harmful. In addition, fructose is sweeter to the taste.

But there's a downside: the liver converts fructose very efficiently into fat. People who consume too much high-fructose food can in time become overweight and develop high blood pressure, dyslipidaemia with fatty liver and insulin resistance—symptoms that doctors group together under the name metabolic syndrome.

## Unchecked growth of the heart muscle

A new paper by Krek and his team member Peter Mirtschink describes a further, more troubling side effect of fructose. The researchers have discovered a previously unknown molecular mechanism that points to fructose as a key driver of uncontrolled growth of the [heart](#) muscle, a condition that can lead to fatal heart failure. Their study was recently published in *Nature*.

When a person has high blood pressure, the heart has to grow as it is harder to pump the blood through the circulatory system. These growing [heart muscle](#) cells require a considerable amount of oxygen. However, since not enough oxygen is available to adequately supply the increased growth, the cells switch to an alternative energy supply. Instead of

drawing energy from fatty acids, they rely more on an anaerobic process called glycolysis—literally, the 'splitting of sugars'. If the heart muscle cells can access fructose in addition to glucose, this can set off a fatal chain reaction.

## **Flipping the switch for fructose metabolism**

In the study, Krek's research group demonstrates that a lack of oxygen in the heart cells cues the appearance of the HIF molecule. This is a universal molecular switch that flips whenever a pathological growth process is under way, such as cardiac enlargement or cancer. HIF causes the heart muscle cells to produce ketohexokinase-C (KHK-C), the central enzyme in fructose metabolism. KHK-C has a high affinity for fructose and can therefore process it very efficiently. The production of KHK-C also has a reinforcing effect on glycolysis. Since fructose metabolism doesn't involve any negative feedback regulation, a vicious cycle starts that can lead to [heart failure](#).

To investigate this mechanism, the researchers used not only mouse models but also biological samples from patients with pathological heart enlargement accompanied by a narrowing of the aortic valve. Samples of [heart muscle cells](#) taken by surgeons during heart operations provided the ETH researchers with the means for proving that such cells really do have more HIF and KHK-C molecules. In mice that were suffering from chronic high blood pressure, the researchers turned off the KHK enzyme, which indeed inhibited enlargement of the heart.

## **One gene, two enzymes**

Another fact worthy of note is that the body also contains KHK-A, an enzyme very similar to KHK-C except that it has poor preference for fructose. Both these enzymes have the same genetic code; the difference

between them comes from how a molecular cutting tool tailors their construction blueprint—their messenger RNA, which is a transcript of the relevant gene. Depending on requirements, one of two blueprints can be generated from the same gene to produce either of two different enzymes. The expert term for this process is 'alternative splicing'. Krek explains, 'About 95 percent of all human genes are alternatively spliced. It's a major way to create the extraordinary variety of proteins, enzymes and regulators in the human body.'

Normally primarily liver cells produce the fructose-friendly KHK-C enzyme; other organs produce almost exclusively KHK-A. Now for the first time, the ETH researchers are showing that even an organ like the heart is capable of producing KHK-C, the more efficient of the two enzymes, if it is exposed to pathogenic stress factors. In the process, HIF activates the molecular cutting tool, or splicing factor, SF3B1. This molecule is often genetically altered in many types of cancer, which possibly indicates that even the growth of cancer can be affected by fructose.

## **Normal fruit consumption safe**

Large volumes of fructose are added to many foods, but especially to sweet beverages and soft drinks. This practice drove up per capita consumption of high fructose corn syrup in the USA between 1970 and 1997, from 230 grams per year to over 28 kilograms.

But Mirtschink provides reassurance that eating a normal amount of fruit daily is safe and healthy. 'Besides fructose, fruit contains plenty of important trace elements, vitamins and fibre,' he says. People should, however, avoid overly sweet [soft drinks](#) and fruit juices—these often have sugar added—as well as ready-made meals and other foods to which large amounts of fructose are added as a flavour carrier. 'Just this surplus of fructose can help trigger the mechanism we have described if

one of the stress factors is present, such as cardiac valve disease or [high blood pressure](#),' Mirtschink emphasises.

**More information:** Mirtschink P et al. HIF-driven SF3B1 induces KHK-C to enforce fructolysis and heart disease. *Nature*, advanced online publication, June 17th 2015. [DOI: 10.1038/nature14508](https://doi.org/10.1038/nature14508)

Provided by ETH Zurich

Citation: Fructose powers a vicious circle (2015, June 17) retrieved 25 April 2024 from <https://medicalxpress.com/news/2015-06-fructose-powers-vicious-circle.html>

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