Scientists develop a novel radiotracer for earlier detection of disease

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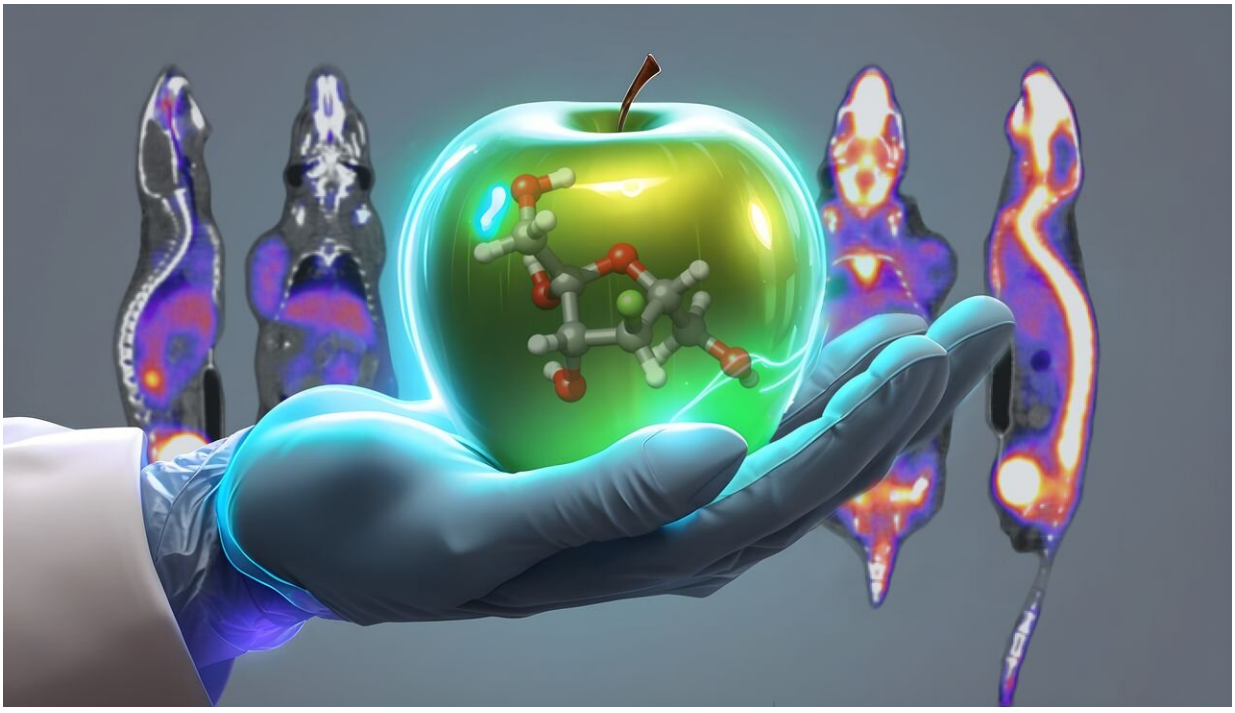

Fructose metabolism has been implicated in various diseases, including metabolic disorders, neurodegenerative disorders, cardiac disorders, and cancer. However, the limited availability of a quantitative imaging radiotracer has hindered its exploration in pathology and diagnostic imaging. Methods: We adopted a molecular design strategy based on the catalytic mechanism of aldolase, a key enzyme in fructolysis. We successfully synthesized a radiodeoxyfluorinated fructose analog, [^{18}F]4-fluoro-4-deoxyfructose ([^{18}F]4-FDF), in high molar activity. Results: Through heavy isotope tracing by mass spectrometry, we demonstrated that C_4-deoxyfluorination of fructose led to effective trapping as fluorodeoxysorbitol and fluorodeoxyfructose-1-phosphate

in vitro, unlike C_1- and C_6-fluorinated analogs that resulted in fluorolactate accumulation. This observation was consistent in vivo, where [^{18}F]6-fluoro-6-deoxyfructose displayed substantial bone uptake due to metabolic processing, whereas [^{18}F]4-FDF did not. Importantly, [^{18}F]4-FDF exhibited low uptake in healthy brain and heart tissues, known for their high glycolytic activity and background levels of [^{18}F]FDG uptake. [^{18}F]4-FDF PET/CT allowed for sensitive mapping of neuro- and cardioinflammatory responses to systemic lipopolysaccharide administration. Conclusion: Our study highlights the significance of aldolase-guided C_4 radiodeoxyfluorination of fructose in enabling effective radiotracer trapping, overcoming limitations of C_1 and C_6 radioanalogs toward a clinically viable tool for imaging fructolysis in highly glycolytic tissues. Credit: *Journal of Nuclear Medicine* (2024). DOI: 10.2967/jnumed.123.266905

The vast majority of positron emission tomography (PET) imaging systems map out how the body uses a radioactive form of glucose for energy. Since many cancers use glucose as a metabolic fuel, they light up on glucose PET scans. However, not all cancers use glucose as fuel, and some normal organs, like the brain and heart, use high amounts of glucose, too, making it difficult to identify some diseases from this type of diagnostic scan.

Now, scientists at the University of Ottawa (uOttawa) have developed a new radiotracer (called [^{18}F]4-FDF) that can map how cells use fructose for energy. Fructose is a different type of metabolic fuel that is increasingly being recognized as a fuel for disease. Fructose, a monosaccharide known as "fruit sugar," is a common dietary sugar found naturally in fruit, honey, and processed foods.

Unlike glucose, fructose is not normally used for fuel by the healthy brain and heart, appearing mostly in healthy liver and kidneys. By identifying where fructose is being used in the body, [^{18}F]4-FDF will

allow for earlier detection of a wide range of diseases, including cancers, as well as inflammation of the heart and brain.

The research was conducted in the Molecular Medicine Lab at uOttawa under Associate Professor Adam Shuhendler from uOttawa's Faculty of Science, who is also a scientist at the University of Ottawa Heart Institute, in collaboration with uOttawa professors Robert Ben and Christina Addison.

Lead author Alexia Kirby, who is a doctoral student in biology, was responsible for validating and testing the radiotracer across various cell and animal models, while Nicholas Calvert, a doctoral student in chemistry and biomolecular sciences, used carbon isotope labeling to determine the metabolic pathway of the radiotracer in cells. The synthetic chemistry was developed by colleagues Rob Ben, Thomas Charlton, and Mojmir Suchy, while Dominic Graf and Mojmir Suchy handled the radiochemistry.

"For the first time, we can see where fructose, a common dietary sugar, is used in the body. Outside of the kidneys and the liver, fructose metabolism in any other organs may point to a sinister problem, including cancer and inflammation," explains Professor Shuhendler.

The [^{18}F]4-FDF compound is made of a carefully modified form of fructose that incorporates a radioactive fluorine atom at a key chemical position, allowing researchers to track where and how much fructose is metabolized in our bodies. Through imaging with a PET camera, a tool that is routinely used in diagnostic imaging, observers can see the increased fructose used by malfunctioning organs and tissues, providing early indications of inflammation.

This discovery opens up new avenues for the earlier detection and care of cancers, as well as brain and heart conditions.

The study is published in the *Journal of Nuclear Medicine*.

More information: Alexia Kirby et al, It's a Trap! Aldolase-Prescribed C4Deoxyradiofluorination Affords Intracellular Trapping and the Tracing of Fructose Metabolism by PET, *Journal of Nuclear Medicine* (2024). DOI: 10.2967/jnumed.123.266905

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