A spoonful of fat makes the medicine go down

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For years scientists and dieticians have argued over the health benefits of dietary fat. Research published this week, however, shows that piggybacking onto natural fat absorption pathways can dramatically enhance the utility of some drugs.

One of the key goals of drug development has long been to produce a therapy that can be taken orally (therefore cheap and easy to deliver) and is absorbed as directly and quickly into the blood stream as possible.

Many medications, however, are broken down in the liver before even making it into the blood stream. This is called "first past metabolism" whereby the drugs we swallow go via the gut and the liver (where breakdown occurs) before even entering the blood.

Scientists have long tried to bypass this process since it can prevent enough drug getting to the site of action to be useful.

Researchers at the ARC Centre of Excellence in Convergent Bio-Nano Science (CBNS) in Melbourne, Australia, have published a patented technology that allows orally administered drugs to by-pass the liver. This technology makes use of a natural nano-scale lipid transport system that delivers drug from the gut through the lymphatic system, and straight into the blood stream.

The publication, in the prestigious European journal, *Angewandte Chemie International Edition*, has been tested on testosterone in animal

models, but, according to Professor Chris Porter, from CBNS, the technology has the potential to be used for a range of drugs that struggle to get through the liver and into the circulation, as well as for drugs targeted to the lymphatic system.

According to Professor Porter, the liver is a marvelous organ for filtering and protecting the body from materials it regards as foreign and breaking them down before they can be toxic. While this is a great advantage when protecting the body from dangerous toxins, it can severely limit the amount of a drug that reaches the site of action after oral administration. "No matter how good the drug is, it needs to be absorbed (into the bloodstream) and to avoid this first pass metabolism in order to get to the general circulation where it acts," he said.

Professor Porter and his team from the CBNS at the Monash Institute of Pharmaceutical Sciences, have been fine tuning what is called a pro-drug technology. Aimed specifically at targeting drug absorption to the lymphatic system (rather than the hepatic portal blood) this technology modifies drugs so that they chemically mimic dietary lipids. Unlike most nutrients, after absorption lipids are assembled into nano-sized lipid droplets or lipoproteins and transported to the circulation via the lymph.

According to Professor Porter the pro-drug technology has two main benefits. "Firstly, the lymphatics drain directly into the blood and do not pass through the liver. This can dramatically enhance the efficiency of drugs with first pass metabolism problems like testosterone," he said.

"Second, the lymphatic system is a key part of the immune system and helps fight disease and regulates the immune response to infection. Drug delivery directly into the lymph may therefore enhance the utility of drugs that are designed to stimulate the immune system to eg fight cancer, or to suppress the immune system to fight autoimmune diseases such as Crohn's Disease".

Using testosterone, as a test drug, the researchers have found that their new delivery system boosts uptake of the drug into the intestinal lymphatics and in the case of testosterone leads to blood levels up to 90 times higher than that possible with the current commercial product. "The advantage of our system is that drugs are shielded from degradation in the liver but are ultimately released when they reach their site of action, ensuring that the drug given to the patient goes where it is supposed to," Professor Porter said.

More information: Luojuan Hu et al, Glyceride-Mimetic Prodrugs Incorporating Self-Immolative Spacers Promote Lymphatic Transport, Avoid First-Pass Metabolism, and Enhance Oral Bioavailability, *Angewandte Chemie International Edition* (2016). DOI: 10.1002/anie.201604207

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