Nanoparticle 'wrapper' delivers chemical that stops fatty buildup in rodent arteries

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In what may be a major leap forward in the quest for new treatments of the most common form of cardiovascular disease, scientists at Johns Hopkins report they have found a way to halt and reverse the progression of atherosclerosis in rodents by loading microscopic nanoparticles with a chemical that restores the animals' ability to properly handle cholesterol.

Cholesterol is a fatty substance that clogs, stiffens and narrows the blood vessels, greatly diminishing their ability to deliver blood to the heart muscle and the brain. The condition, known as atherosclerotic vessel disease, is the leading cause of heart attacks and strokes that claim some 2.6 million lives a year worldwide, according to the World Health Organization.

A report on the work, published online in the journal *Biomaterials*, builds on recent research by the same team that previously identified a fat-and-sugar molecule called GSL as the chief culprit behind a range of biological glitches that affect the body's ability to properly use, transport and purge itself of vessel-clogging cholesterol.

That earlier study showed that animals feasting on high-fat foods remained free of heart disease if pretreated with a man-made compound, D-PDMP, which works by blocking the synthesis of the mischievous GSL.

But the body's natural tendency to rapidly break down and clear out D-PDMP was a major hurdle in efforts to test its therapeutic potential in

larger animals and humans.

The newly published report reveals the scientists appear to have cleared that hurdle by encapsulating D-PDMP into tiny molecules, which are absorbed faster and linger in the body much longer. In this case, the researchers say, their experiments show that when encapsulated that way, D-PDMP's potency rose ten-fold in animals fed with it.

Most strikingly, the team reports, the nano version of the compound was potent enough to halt the progression of atherosclerosis. By contrast, the team's previous research showed the drug was effective in preventing atherosclerosis but not potent enough to stop the disease from advancing. Perhaps, most importantly, the team says, the nano-packaged drug improved physiologic outcomes among animals with heart muscle thickening and pumping dysfunction, the hallmarks of advanced disease.

"Our experiments illustrate clearly that while content is important, packaging can make or break a drug," says lead investigator Subroto Chatterjee, Ph.D., a professor of medicine and pediatrics at the Johns Hopkins University School of Medicine and a metabolism expert at its Heart and Vascular Institute. "In our study, the right packaging vastly improved the drug's performance and its ability not merely to prevent disease but to mitigate some of its worst manifestations."

That added potency, the researchers say, stems from fast uptake by various tissues and organs and from the slow clearance of the encapsulated form of the drug.

The team was able to map and track the nanoparticles' movement inside the animals' bodies by tagging them with a radioactive tracer that lit up on a CT scan.

Next, to observe how quickly the body broke down the nano-wrapped

and the original forms of the drug, researchers analyzed kidney samples from mice treated with either form of the compound. The kidneys are the final stop on most drugs' journey inside the body just before they are cleared through urine. The nano drug remained in animals much longer, around 48 hours, compared with the free form, which was excreted through the kidneys in about an hour.

In further experiments, the scientists put mice genetically predisposed to atherosclerosis on a fat-laden diet for several months—long enough for fatty plaque to accumulate inside their blood vessels. After a few months, a third of the animals began treatment with the nano-packaged compound, one-third with its native version, while the rest got placebo.

Mice treated with placebo showed high levels of GSL—the molecule responsible for altered cholesterol metabolism—and high levels of bad cholesterol, or LDL. They also had dangerously high levels of oxidized LDL, an especially pernicious type of LDL formed when it encounters free radicals, and elevated triglycerides, another type of plaque-building fat. By contrast, animals given encapsulated D-PDMP had normal GSL and cholesterol levels as did animals treated with free-floating forms of the drug. However, animals treated with the free-floating form of D-PDMP required 10 times higher doses to achieve GSL and cholesterol levels observed in mice given the nano-encapsulated form of the drug.

When scientists measured the thickness of the animals' aortas—the body's largest vessel responsible for carrying oxygen-rich blood from the heart to the rest of the body—they observed stark differences among the groups, they say.

The aortas of placebo-treated animals had grown thicker with fat and calcium deposits. Mice treated with either version of the drug fared better, but animals that got the encapsulated form of the drug had aortas nearly indistinguishable from the aortas of healthy mice fed a regular

diet, according to researchers.

Most strikingly, they reported, D-PDMP treatment improved heart function in mice with advanced forms of atherosclerotic heart disease, marked by heart muscle thickening and compromised pumping ability. Ultrasound images revealed that both size and pumping ability improved in animals that received treatment with the encapsulated form of the drug, returning to near baseline levels. However, mice given non-encapsulated drug required 10 times higher doses to achieve similar benefits.

High cholesterol occurs when the body gets too much of it from food, when it makes too much of it on its own, or due to a defect in the body's ability to ferry it in and out of cells or break it down.

Current cholesterol-lowering treatments work either by blocking cholesterol production or by preventing the body from absorbing too much of it. But production and absorption are only two steps in the cholesterol cycle, Chatterjee says, so new treatments that interfere with other glitches in this cycle are badly needed. D-PDMP is one such treatment candidate because it blocks the synthesis of GSL—the master regulator of multiple pathways involved in faulty fat metabolism, Chatterjee says.

Researchers say their next step is to test how the drug performs in larger mammals. Because the nanoparticles carrying D-PDMP are made of a common laxative ingredient and a naturally occurring sebacic acid, researchers say they are completely safe for humans. D-PDMP, long used in basic research to experimentally block and study cell growth and other basic cell functions, is considered safe in animals, but its safety profile in humans is unknown, the investigators say.

Provided by Johns Hopkins University School of Medicine