Goat Pharm at Johns Hopkins

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New compound controls weight and blood sugar in mice

Newswise — Johns Hopkins scientists report success in significantly lowering levels of both fat mass and blood sugar in mice treated with a chemical compound designed to disrupt production of a hormone known to stimulate weight gain in humans.

Their new synthetic amalgam, dubbed GO-CoA-Tat, was shown to control weight and glucose in mice by effectively stalling GOAT (ghrelin O-acyltransferase), an enzyme that revs up the manufacture of acyl-ghrelin, the form of the hormone that affects weight gain and blood sugar. The research appears online Thursday, Nov. 18, in Science.

Early research on ghrelin, discovered just a decade ago, indicated that the hormone might work as an appetite stimulant. However, more recent studies, including this one, suggest its primary mode of action might be on metabolism.

“Our experiments show not only that this new enzyme inhibitor is surprisingly potent, but also that it doesn’t seem to change food intake, arguing against an appetite effect and for a metabolism effect,” says Philip A. Cole, M.D., Ph.D., Marshall-Maren Professor and director of the Department of Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine. “Both our cellular and animal studies demonstrate the exciting potential for this approach, but there’s a lot more work to be done to develop this into a drug that would help patients.”

The Hopkins team designed their compound to fit snugly into the active region of the enzyme that brings together ghrelin and a fatty acid. By occupying that space, it effectively blocks the normal chemical binding that results in the production of GOAT, the enzyme that makes acyl-ghrelin. Because GOAT is inside of cells, and not easily reachable, the researchers also attached to the compound a chemical bit called TAT, which helps cargo to penetrate cells.

It was relatively straightforward for the team, which has expertise designing drugs related to enzymes, to assemble all the important features of a GOAT inhibitor, Cole says, adding that the real challenge was measuring acyl-ghrelin, a key to demonstrating the compound’s effectiveness.

To test the new compound, the team engineered Hela cells to make lots of acyl-ghrelin. Then they added their new compound, the GOAT inhibitor, to the dish in which the cells were living. After waiting several hours, they broke open the cells and measure the levels of acyl-ghrelin hormone.

The GOAT inhibitor significantly reduced the levels of acyl-ghrelin, but did not affect the levels of its precursor. “That’s the all-important step we wanted to hit,” Cole says, “because it’s vital in activating ghrelin as a hormone that controls weight and blood sugar.”

Next, the researchers injected the GOAT inhibitor into the abdomens of live mice. Blood samples up to 24 hours after a single dose showed that acyl-ghrelin levels were reduced.

Finally, the team conducted both short- and long-term studies in both wild-type mice and those genetically altered to be deficient in ghrelin in order to determine the effects of the GOAT inhibitor on their weight and blood sugar.

After injecting both normal mice and so-called ghrelin knockout mice engineered to be unable to make active ghrelin with the GOAT inhibitor, the team waited 24 hours before challenging all the animals with a glucose load test analogous to the glucose tolerance test used in humans to diagnose diabetes. Those normal mice pretreated with the GOAT inhibitor showed up to a 40 percent reduction in blood sugar levels compared with untreated animals. As expected, GOAT inhibitor did not affect the ghrelin knockout mice.
In a monthlong experiment, one normal group and one ghrelin knockout group of mice was injected with the GOAT inhibitor once daily. Their weights were measured daily, and fat and lean body mass were measured every few days. After about one month, the treated normal mice showed statistically significant relative reduction in fat mass/total mass — about 10 percent total and 30 percent fat mass — but there was no change in lean mass. By month’s end, the treated normal mice were shown to have lower average blood-sugar levels than untreated animals. Again, the GOAT inhibitor did not affect the ghrelin knockout mice, showing that the GOAT inhibitor acts specifically on ghrelin synthesis and no other metabolic pathway.

“The long-range hope is that compounds of this type will be useful to overweight patients as well as those with diabetes,” Cole says. “It may well be complementary to other approaches that are also in the research stage.”

The study was supported by the NIH, Pfeiffer Foundation, Kaufman Foundation, and Keck Foundation.

Phil Cole is a cofounder and advisor of Acylin Therapeutics Inc. Acylin has recently in-licensed GOAT and p300/CBP HAT technologies from JHU.

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On the Web:
Phil Cole discusses GOAT Pham on youtube: [http://www.youtube.com/watch?v=hbMPOECBI_U](http://www.youtube.com/watch?v=hbMPOECBI_U)
Phil Cole: [http://www.hopkinsmedicine.org/pharmacology/research/cole.html](http://www.hopkinsmedicine.org/pharmacology/research/cole.html)
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