Obese monkeys lose weight on drug that attacks blood supply of fat cells

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Obese rhesus monkeys lost on average 11 percent of their body weight after four weeks of treatment with an experimental drug that selectively destroys the blood supply of fat tissue, a research team led by scientists at The University of Texas MD Anderson Cancer Center reports in *Science Translational Medicine*.

Body mass index (BMI) and abdominal circumference (waistline) also were reduced, while all three measures were unchanged in untreated control monkeys. Imaging studies also showed a substantial decrease in body fat among treated animals.

"Development of this compound for human use would provide a non-surgical way to actually reduce accumulated white fat, in contrast to current weight-loss drugs that attempt to control appetite or prevent absorption of dietary fat," said co-senior author Renata Pasqualini, Ph.D., professor in MD Anderson's David H. Koch Center for Applied Research of Genitourinary Cancers.

Previous attempts to treat obesity have predominantly focused on drugs aimed at suppressing appetite or increasing metabolism, the researchers noted, but these efforts have been hampered by their toxic side-effects. The MD Anderson group designed a new drug, which includes a homing agent that binds to a protein on the surface of fat-supporting blood vessels and a synthetic peptide that triggers cell death. Their blood supply gone, fat cells are reabsorbed and metabolized.

"Obesity is a major risk factor for developing cancer, roughly the equivalent of tobacco use, and both are potentially reversible" said co-senior author Wadih Arap, M.D., Ph.D., also professor in the Koch Center. "Obese cancer patients do worse in surgery, with radiation or on chemotherapy -- worse by any measure."

Monkeys are spontaneously obese

In earlier preclinical research, obese mice lost about 30 percent of their body weight with the drug, now called Adipotide. The drug acts on white adipose tissue, the scientific name for the unhealthy type of fat that accumulates under the skin and around the abdomen, and is a disease and mortality predictor.

"Most drugs against obesity fail in transition between rodents and primates," Pasqualini said. "All rodent models of obesity are faulty because their metabolism and central nervous system control of appetite and satiety are very different from primates, including humans. We're greatly encouraged to see substantial weight loss in a primate model of obesity that closely matches the human condition."

The rhesus monkeys in the current study were "spontaneously" obese, said study first author Kirstin Barnhart, D.V.M, Ph.D., a veterinary clinical pathologist at MD Anderson's Keeling Center for Comparative Medicine and Research in Bastrop, Texas. No specific actions were taken to make them overweight; they became so by overeating the same foods provided to other monkeys in the colony and avoiding physical activity.

The wider problems of obesity

This primate model also shares other physiological features associated

with human obesity, such as metabolic syndrome, characterized by an increased resistance to insulin, which can lead to the development of type 2 diabetes and cardiovascular disease. Adipotide-treated monkeys showed marked improvements in insulin resistance — using about 50 percent less insulin after treatment.

Arap, Pasqualini and colleagues are preparing for a clinical trial in which obese prostate cancer patients would receive daily injections of Adipotide for 28 consecutive days. "The question is, will their prostate cancer become better if we can reduce their body weight and the associated health risks," Arap said.

Some prostate cancer treatments, such as hormone therapy, cause weight gain. Greater weight can lead to arthritis, which in turn causes inactivity that leads to more weight gain, a cascade effect of co-morbidities, Arap said. Fat cells also secrete growth hormones that cancer cells thrive upon.

Overall and abdominal body fat levels drop, with reversible renal side effects

Weight, BMI and abdominal circumference all continued to drop for three weeks after treatment ended before slowly beginning to reverse during the fourth week of the follow-up period.

Magnetic Resonance Imaging (MRI) was used to gauge abdominal body fat, thought to be the most dangerous area for humans to gain weight in terms of raising disease risk. Treated monkeys' abdominal fat levels fell by 27 percent during the study. Fat levels increased slightly in the control group.

Lean monkeys did not lose weight in a separate study to test for potential effects of the drug in non-obese animals, indicating that the drug's effect

may be selective for obese subjects.

Monkeys in the studies remained bright and alert throughout, interacting with caretakers and demonstrating no signs of nausea or food avoidance. This is potentially an important finding since unpleasant side-effects have limited the use of approved drugs that reduce fat absorption in the intestines.

The principal side effects were noted in the kidneys. "The renal effect was dose-dependent, predictable and reversible," Barnhart noted.

Second drug developed via vascular ZIP codes

This study is the second drug developed using a vascular mapping technique created by the Arap-Pasqualini lab. Blood vessels, they found, are more than a uniform and ubiquitous "pipeline" that serves the circulatory system, but differ depending on the organ or tissue that they support.

They have developed a way of screening peptides – small bits of proteins – to identify those that bind to specific vascular cells among the many possible "ZIP codes" present in a human vascular map. For blood vessels that support fat cells, the target protein is prohibitin, which they found in unusual abundance on the blood vessel cell surface.

"The same delivery system used in mice and monkeys was recently validated in human white fat, as reported recently by our group," Arap said.

An earlier drug, which uses a different molecular address to target the blood supply of prostate cancer, has been evaluated in a first-in-man clinical trial, just completed at MD Anderson.