SOUTHWESTERN NEWS

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TOO MUCH FAT IN HEART CELLS CAN CAUSE HEART FAILURE, RESEARCHERS FIND DIABETES DRUG MAY HELP

DALLAS – February 15, 2000 – A study of genetically obese rats has revealed that an overabundance of fat can collect in heart cells and cause them to die, UT Southwestern Medical Center at Dallas researchers report. The scientists also found that a diabetes drug prevents this damage, which can lead to heart failure.

The researchers' findings are significant because the incidence of obesity in children has greatly increased in the United States in recent years. The scientists believe that if fat droplets accumulate in the same way in humans -- causing the dysfunction and death of myocytes, or heart cells -- then in 20 or 30 years this form of heart disease, called lipotoxicity, will reach staggering proportions.

The research, published in today's issue of *Proceedings of the National Academy of Sciences*, also found that the diabetes drug Troglitazone prevented lipotoxic heart disease in the rats by oxidizing the fat so it burns up rather than accumulating and causing heart-cell death.

"This cell death in the heart is a consequence of the presence of more fat than is required for producing energy," said Dr. Roger Unger, director of UT Southwestern's Touchstone Diabetes Center.

The work was done in collaboration with a laboratory headed by Dr. Lelio Orci, chairman of morphology at the University of Geneva Medical School.

"Although this research was in genetically abnormal rats, we have reason to believe that this same process occurs in people," Orci said.

The rat model used in the study had an abnormal leptin receptor. Unger and others previously found that leptin, a hormone that is greater in obese individuals, prevents the flow of fat into nonfat cells. In the pancreas, this overflow of lipids caused the death of islet cells that produce insulin, which results in the development of type II diabetes, or non-insulin dependent diabetes mellitus.

The investigation showed that fat accumulation in the heart triggers apoptosis, or cell death, just as it did in the pancreas. The researchers studied the rats' cardiac muscles using an echocardiogram and then with an electromicroscope in biopsies.

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As the myocytes died, the left ventricle of the heart became unable to contract properly, indicating the organ was developing cardiomyopathy, or heart failure.

"This damage occurs fairly early because, unlike other organs, the heart has a finite number of muscle cells; they can't proliferate," said study co-author Dr. Paul Grayburn, professor of internal medicine at UT Southwestern and chief of cardiology at the Dallas Veterans Affairs Medical Center. "Even if you lose only 20 percent of the myocytes, irreversible damage occurs, and cardiomyopathy will develop."

Fat buildup in the heart happens normally as people age, but scientists believe it happens at a much earlier age in obese people, especially in those who don't exercise.

"We really worry about the current generation of sedentary, obese children," Grayburn said.

Unger, who also heads the Gifford Laboratories for Diabetes Research, said, "If you run marathons until you're 85, you probably won't develop lipotoxic heart disease."

Next the scientists will use another strain of rats, ones that have been purposely overfed to cause obesity, to determine if the fat buildup causes lipotoxicity and heart dysfunction.

In addition, the investigators are working with colleagues in UT Southwestern's Donald W. Reynolds Cardiovascular Clinical Research Center and the UT Southwestern Department of Radiology to develop a method to measure myocardial fat in people using magnetic resonance imaging (MRI) techniques.

The Reynolds Center was established recently to translate discoveries of this type into clinical application in order to lower heart disease.

"Because this is a completely preventable condition in the obese rats, I believe it is urgent to find out if this happens in humans," Unger said. "If it does, we may already have the drug to treat it."

The other researchers involved in this study were Dr. Yan-Ting Zhou, formerly with Gifford Laboratories and now a resident at St. Paul Medical Center; Dr. Asad Karim, assistant professor of internal medicine and a researcher at the VA; Drs. Michio Shimabukura and Moritake Higa, postdoctoral fellows in internal medicine; and Dr. Dany Baetens of the University of Geneva Medical School.

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