Body-weight regulation scientists give perspective on obesity-related research

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When obesity overloads the body with excess nutrients, parts start to fail. Obesity contributes to heart disease, stroke, diabetes, high blood pressure, some cancers, liver disease, immune dysfunction, painful joints, and a host of other problems. With so many parts of the body affected, studies of the health effects of obesity that concentrate on one body organ or system may overlook common underlying events occurring at the cellular level throughout the body.

A "Perspective" article on obesity research appearing in the Nov. 9, 2007 issue of *Science* proposes that a broader approach is needed to uncover the causes and consequences of obesity.

The authors of the Science article, "An Integrative View of Obesity," are body-weight regulation researchers Dr. Brent E. Wisse, Dr. Francis Kim, and Dr. Michael Schwartz. Wisse is University of Washington (UW) assistant professor of medicine and Schwartz is a professor of medicine, both in the Division of Metabolism, Endocrinology, and Nutrition. Kim is an associate professor of medicine, Division of Cardiology. All are UW Medicine physicians at Harborview Medical Center in Seattle. Next year the authors will be members of the new UW Medicine Diabetes and Obesity Center of Excellence, directed by Schwartz.

The authors point to work by Dr. Gökhan S. Hotamisligil of the Harvard University School of Public Health and others who have proposed that metabolic problems arise when the body's cells have to deal with an excess of nutrients. An excess occurs when the body consumes more

energy in food than it needs to meet ongoing energy requirements. Hotamisligil and other scientists have found that the oversupply triggers several similar, harmful responses in a variety of cell types: liver cells, the cells lining blood vessels, muscle cells, immune cells and even brain cells.

According to the Science Perspective article, identifying similarities in how different kinds of cells respond to excess nutrients might reveal why so many people put on too much weight and then are unable to lose it.

The body, the authors said, actively protects its fat stores. Obesity results not through passive accumulation of excess fat, but through the defense of elevated levels of body fat. Deciphering the causes of obesity, they noted, would have to take this defense of fat stores into account. Working out the patterns of cell responses to excess nutrients might, the authors said, also reveal why overeating and obesity lead to so many diseases. This information might also explain why animals on a calorie-restricted diet live longer.

Researchers around the world are beginning to see pieces of the patterns of how cell respond to excess nutrients. Among the ways cells react is to produce too many molecules called reactive oxidative species. These molecules create trouble called oxidative stress. The oxidative stress can damage cell structures. Nutrient excess also impedes the final stages of protein production, in which newly made proteins fold into their mature forms inside the cell. The power stations of the cell, the mitochondria, slack off in the presence of excess nutrients, and fatty acid derivatives accumulate. A common endpoint of all these responses is inflammation.

Inflammation, in turn, can block the action of insulin, a hormone that stimulates cells to take up nutrients. The molecules that promote inflammation interfere with cell signaling involved in insulin action. This response protects an individual cell because it limits additional nutrient

uptake. However, as insulin resistance progresses to many cells, and inflammation worsens, more pro-inflammatory molecules arrive, and the cycle becomes difficult to break, the authors note.

Scientists in several labs have data that suggest that nerve cell responses to excess nutrients might interfere with insulin and other appetite control signals to the brain. The brains of rodents fed a tasty, energy-rich diet, even for a short time, show an impaired response to insulin and other appetite control signals. The rodents' brain cells display inflammation and insulin resistance similar to that seen in other types of cells. These events may render their brains unable to notice that their bodies packing away fat reserves, and therefore their brains don't suppress their appetites. Instead the rodents act hungry and eat more.

Nutrient excess also leads to inflammation of the pancreatic cells that produce insulin, according to several studies. The authors wonder if this might help to explain how impaired insulin secretion, coupled with the demand for more insulin created by insulin resistance, sets the stage for Type 2 diabetes.

The authors also cite work performed by UW cardiologist Francis Kim indicating how the lining of blood vessels might respond to excess nutrients. This response may inhibit the signals that control the manufacture of nitric oxide, so that production drops. Nitric oxide is needed for blood vessels to expand to let blood flow normally. The response also induces inflammation of the blood vessel lining. This, the authors say, could be a plausible link between excess nutrients and common heart and blood vessel diseases.

The authors emphasize that this particular sequence of events is not the only key to understanding obesity and its resulting medical problems. However, it illustrates how different kinds of problems in different organs --heart disease, diabetes-- might be partly due to a cellular

response common to many parts of the body.

The authors conclude that more integrative approaches, those that seek out underlying disease mechanisms occurring in cells and tissues throughout the body, rather than those that study single body parts or systems, might more readily lead to strategies for preventing or treating obesity and the many medical problems that accompany it.

Source: University of Washington