The role of lipids in the pathogenesis of metabolic disorders

Toxic Fats

AGNIESZKA DOBRZYŃ
Nencki Institute of Experimental Biology, Warsaw
Polish Academy of Sciences
adobrzyn@nencki.gov.pl

Assoc. Prof. Agnieszka Dobrzyń leads the Laboratory of Cell Signaling and Metabolic Disorders at the Nencki Institute of Experimental Biology. She studies the molecular and biochemical foundations of lipid toxicity, especially the link between obesity and metabolic disorders

The metabolic diseases that pose a major problem for obese individuals are actually not caused by overdeveloped fat tissue. In fact, the culprits turn out to be lipids stored in other tissues, ill adapted to accumulating fat

Obesity has become one of the most rapidly expanding plagues of modern civilization in recent decades, ultimately caused by increased consumption of high-calorie processed foods and sedentary lifestyles. In Poland, 20–30% of the adult population and as many as 8% of children are estimated to be overweight (moderate obesity), while significant obesity occurs in 15–20% of adults and around 5% of children. UK and US statistics are even more alarming: 60% of US society is overweight, with 40% suffering from obesity!

Being overweight or obese are risk factors for many illnesses, including insulin resistance, type 2 diabetes, heart disease, high blood pressure, and fatty liver. The World Health Organization reports that the consequences of these diseases, frequently described as the Metabolic Syndrome, are one of the main causes of death in highly developed countries. Obesity has been dubbed the illness of the 21st century.

What's gone wrong?

Why is it that obese individuals suffer from such metabolic conditions? That question vexes thousands of researchers the world over. Identifying the causes for metabolic disorders in obese individuals could lead to the development of a

One of the main causes of obesity is increased consumption of high-calorie processed foods

Bartosz Ostrowski/BE&W

Bad dietary habits? In Poland, 20–30% of adults and as many as 8% of children are overweight. Still, US and UK statistics are even more alarming!

very much needed new strategy of therapy, enabling obesity-related complications to be effectively prevented and treated.

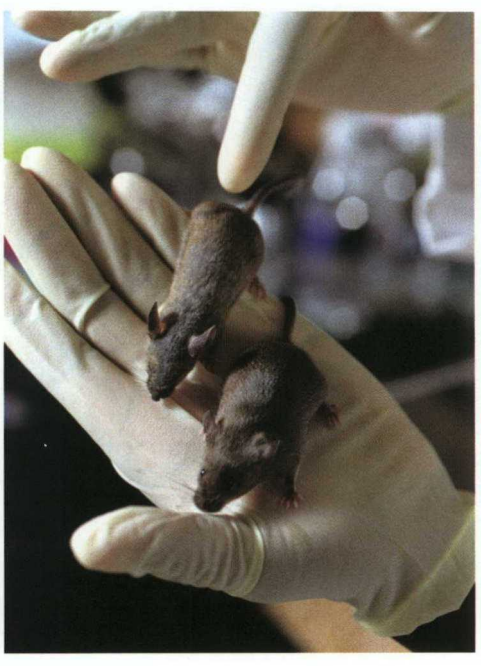
A link between obesity and the conditions that characterize the Metabolic Syndrome has been known to exist for years. Clinical research is conclusive in this regard: just a 10% drop in body mass significantly reduces the risk of atherosclerosis, lowers blood pressure, and increases the insulin sensitivity of tissues. However, the molecular mechanism underlying the incidence of such illnesses as insulin resistance, diabetes, and heart failure in obese individuals is still not fully understood.

For a long time the main cause of the Metabolic Syndrome in obese individuals was thought to be overdeveloped fat tissue (known as adipose tissue), which disturbs the function of other organs by secreting adipocytokines like TNFα or resistin. Yet recent years of research have shown that it is not overdeveloped fat tissue but rather lipids accumulating in such tissues as skeletal muscles, pancreatic β cells, the liver, and cardiac muscle that are the main cause of metabolic diseases in obese individuals. Unlike fat tissue, such tissues are not well adapted to storing fat. The excessive accumulation of free fatty acids and their metabolites has an unfavorable impact on their function. This toxic action of intracellular lipids is now thought to be the immediate cause of obesity-related insulin resistance, diabetes, and heart disease.

In all the wrong places

This breakthrough in our understanding of Metabolic Syndrome pathogenesis was triggered by research on mice genetically modified to be completely devoid of adipose tissue. Lacking such normal fat tissue, these animals accumulated the surplus fat supplied in their diet in other

Jeff Miller



Mice in which the SCD1 gene has been knocked out (left) are immune to obesity and do not suffer from Metabolic Syndrome conditions

Sophie Mullinax, www.sxc.hu

Obesity and being overweight are risk factors for Metabolic Syndrome, the consequences of which the World Health Organization recognizes as one of the main causes of death in highly developed countries

tissues. The accumulation of fat in their organs turned out to be a direct cause of disorders like diabetes, heart failure, and liver disease. Intriguingly, Metabolic Syndrome conditions developed much faster and more acutely in these mice genetically devoid of adipose tissue than they did in obese mice!

Lipid content in non-adipose tissues depends upon a given cell's current demand (which increases, for instance, during physical exercise), and if fatty acid metabolism regulation is working properly lipid content will not exceed the amount that can be used by a given cell (for generating energy, building cell membranes, synthesizing signal compounds, etc.) When there is a higher concentration of lipids in the blood plasma (due to a chronic surplus of consumed food, for instance), the transport of fatty acids into the cell may exceed its actual needs. This triggers compensatory mechanisms that cause excess fatty acids to be removed from the cell though β-oxidation. A leading role in this process is played by hormones secreted by adipose tissue - leptin and adiponectin.

Toxic effects

A problem arises when these compensatory mechanisms break down - most frequently because tissues develop a resistance to leptin and adiponectin, as is frequently seen in obese individuals, or due to a shortage of such hormones, as seen in lipid dystrophy (a lack of adipose tissue) and visceral obesity. Then the excessively accumulated fatty acids and/or their derivatives (ceramides, 1,2 diacylglycerds) and the products of lipid peroxydation disrupt intracellular signaling processes.

The effect of such toxic lipid activity depends on the type of tissue. In pancreatic β cells and cardiomyocytes excessive fat accumulation leads to apoptosis, in skeletal muscles it impedes the insulin pathway, and in the liver it directly causes disturbances in the metabolism of lipoproteins. The best strategy for combating metabolic diseases, therefore, seems to be eliminat-

ing fat from accumulating in tissues that are not adapted for it. But to be able to do that, we need to understand the molecular mechanism regulating the intracellular metabolism of lipids.

Resistant to obesity

Research carried out by a team led by Professor James Ntambi at the University of Wisconsin-Madison in the United States (involving the present author) and subsequently continued at the Laboratory of Cell Signaling and Metabolic Disorders at the Nencki Institute of Experimental Biology in Warsaw (led by the present author) has shown that one of the main factors significantly involved in the intracellular metabolism of lipids and carbohydrates is the activity of stearoyl-CoA desaturase (SCD). SCD1 turns out to be the main target gene of leptin and this hormone's metabolic effect is in large part triggered by the suppression of SCD1 expression.

Mice in which the SCD1 gene has been "knocked out" remain slim despite eating 25% more food than normal mice and do not accumulate fat regardless of their type of diet (including high-fat and high-carbohydrate diets!) Such mice show very high energy expenditure, decreased intracellular lipid content, and increased insulin sensitivity. They are also resistant to obesity triggered by either diet or by leptin deficiency. More importantly, the animals deprived of SCD1 activity do not suffer from the Metabolic Syndrome.

The mechanism by which SCD controls intracellular metabolism is not yet fully understood, but the results obtained so far suggest that drugs that reduce the expression or inhibit the activity of SCD could one day be used in treating obesity, fatty liver, and insulin resistance.

Hopes and challenges

Identifying the mechanism responsible for the development of insulin resistance, diabetes, and cardiovascular diseases in obese individuals and proposing an effective therapy for the Metabolic Syndrome represents one of the greatest challenges for modern medical science.

More and more data now indicate that the toxic lipid action observed in experimental animal models may also underlie the pathogenesis of the Metabolic Syndrome in people. Clinical research points to a close dependency between free fatty acid content on the one hand and insulin resistance, glucose intolerance, hypertriglyceridemia, heart failure, and high blood pressure on the other. Significantly increased lipid content has been identified in the pancreatic β cells of individuals suffering from type 2 diabetes and in the skeletal muscles of individuals with low glucose tolerance. At the same time, the factors that reduce the intracellular accumulation of lipids, like low-calorie diet or physical activity, increase tissue sensitivity to insulin in both obese animals and in people. Pharmacological drugs that effectively eliminate lipotoxic diseases are currently being tested in laboratory animals. Further tests will show whether they are also effective and safe for humans. ■

Further reading:

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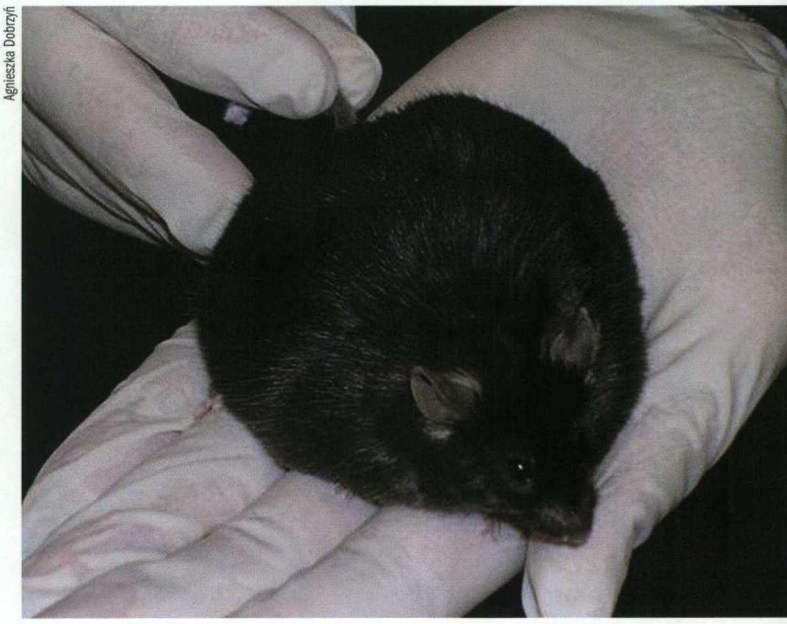

Agnieszka Dobrzyń

Mice with a mutated leptin (ob/ob) gene are one of the most popular experimental models utilized in studies of Metabolic Syndrome pathogenesis