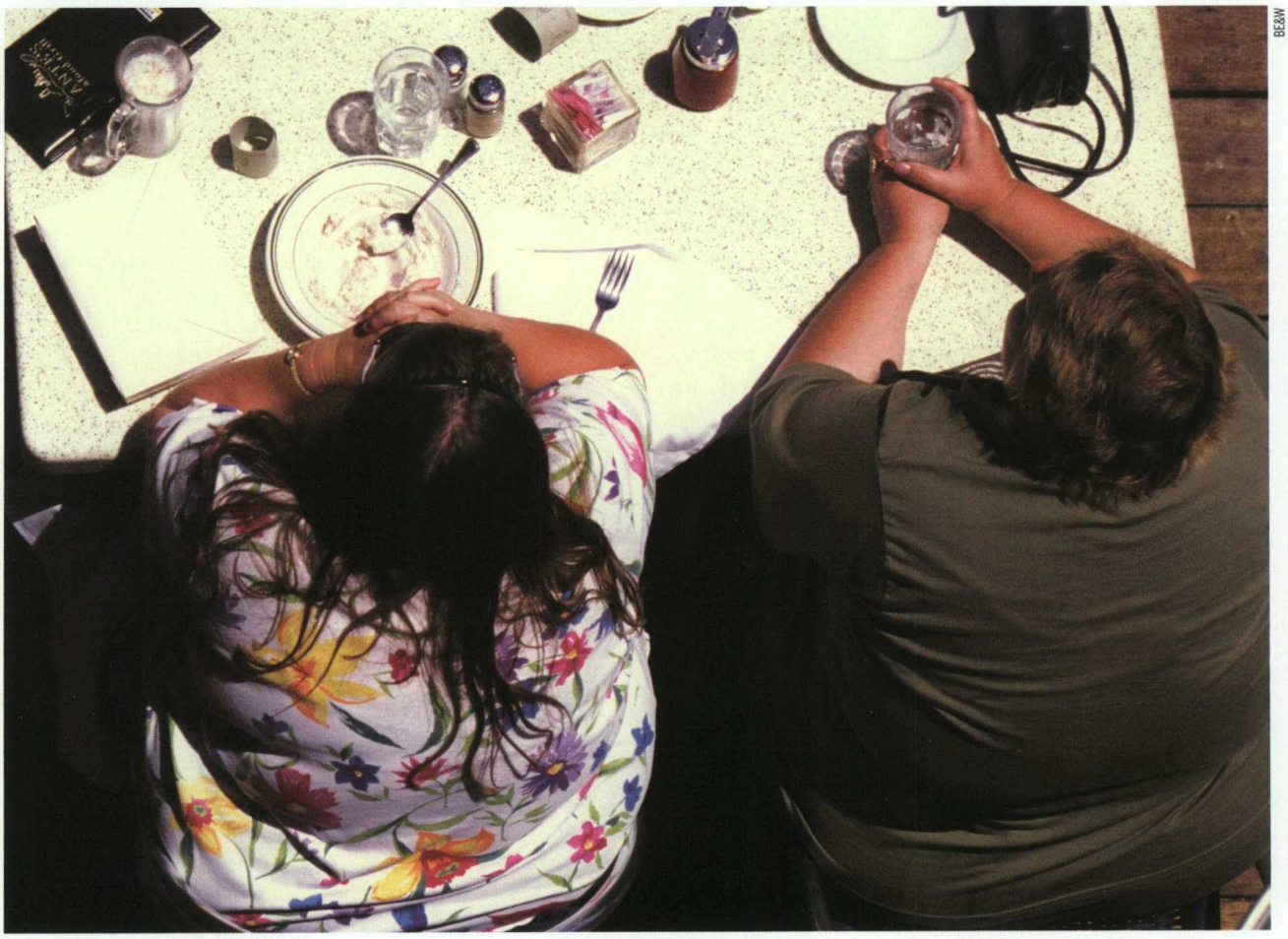
Total Eclipse of the Heart

PAWEŁ DOBRZYŃ
Nencki Institute of Experimental Biology, Warsaw
Polish Academy of Sciences
p.dobrzyn@nencki.gov.pl
Dr. Paweł Dobrzyń studies therapies for obesity-related congestive heart failure. He is a winner of the LIDER Program organized by the Polish National Research and Development Centre

Existing therapies for heart failure do not target intracellular pathways regulating the metabolism of cardiomyocytes, even though research shows that this could offer an effective treatment method

Heart failure occurs when the cardiac muscle cannot provide an adequate blood supply to all tissues and organs. This is caused by impeded systolic and diastolic heart function, which can result from any long-term heart disorder, such as heart attack, coronary disease, valve dysfunction, high blood pressure, as well as other systemic illnesses, such as viral inflammation. This list of main risk factors for heart failure has recently been extended to include obesity.

Existing treatment of heart failure is largely limited to recommending that the patient adapt their lifestyle and eliminate factors that may contribute to the disease's occurrence or progress. Pharmacological treatment includes drugs that slow down the heart, stabilize blood pressure and reduce heart load, as well as others that



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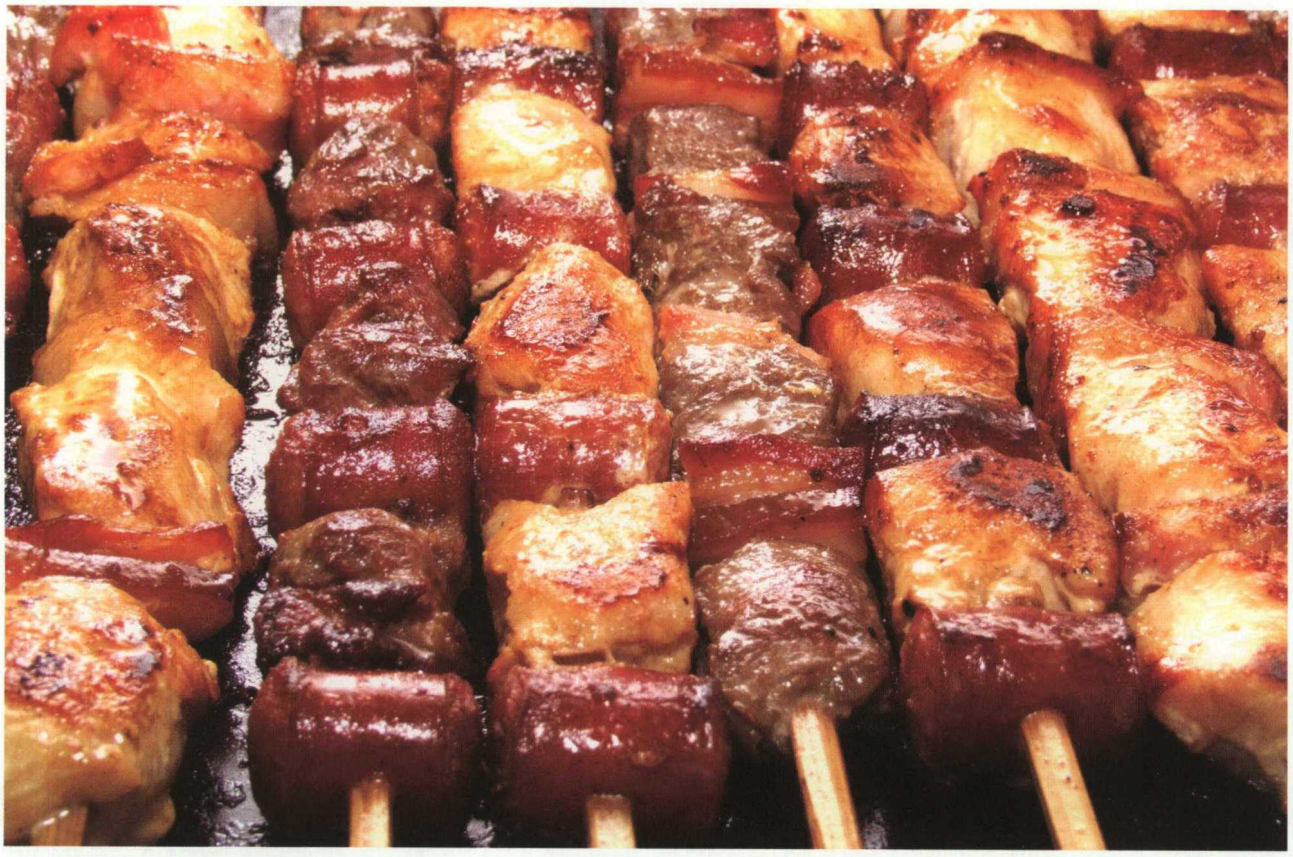
Obesity is one of the main risk factors for heart failure – when the cardiac muscle cannot provide an adequate blood supply to all tissues and organs



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Even with an unhealthy, fat- and carbohydrate-rich diet – such as the human food pictured here – mice in which the SCD1 gene (which codes for one of the main enzymes necessary in the biosynthesis of monounsaturated lipids) is not expressed were not found to accumulate fat

treat illnesses co-occurring with heart failure and are frequently its underlying cause. In certain advanced forms of the disease, when pharmacological treatment has proven ineffective, patients undergo cardiac surgery, including procedures such as coronary artery angioplasty, cardiac resynchronization therapy, permanent implantation of cardioverter-defibrillators, coronary bypass surgery, correction of heart valve disorders, and procedures correcting the size and shape of the left ventricle. Heart transplants may even be considered in extreme and untreatable cases. However, no methods in use today target the intracellular pathways regulating cardiomyocyte metabolism, even though numerous studies indicate that disorders in the metabolism of energy substrates are one of the main causes of congestive heart failure.

Heart disease and obesity

The left ventricle dysfunction that accompanies obesity is traditionally linked to high blood pressure and atherosclerosis leading to heart ischaemia, resulting from high cholesterol and triglycerides levels in the plasma. Research shows that one of the causes of cardiomyopathy linked with obesity may also involve disorders of intracellular lipid metabolism leading to the accumulation of fat on the heart. Excessive accumulation of fatty acids in cardiomyocytes leads to apoptosis of these cells and reduces their sensitivity to insulin; it is likely to be the direct cause of cardiomyopathy accompanying obesity, described as lipotoxic heart disease. There is a growing body of research confirming the negative effects of excessive lipid accumulation on cardiomyocyte function. ECG studies carried out in the Zucker Diabetic Fatty (ZDF) rat model and the ob/ob mouse model (the animals have a mutation in the ob gene, and cannot produce leptin) have shown a significant reduction in left ventricular contractions, resulting from apoptosis of cardiomyocytes caused by disorders of lipid management. The main route leading to cardiomyocyte dysfunction that accompanies lipotoxic heart disease is excessive ceramide accumulation. Ceramides activate apoptosis through the induction of the NFkB transcription factor and increased expression of inducible nitric oxide synthase (iNOS), resulting in increased nitric oxide synthesis. Nitric oxide is a substrate for the synthesis of active oxidants, such as peroxynitrite, which directly induce apoptosis. Another factor in the activation of apoptosis is the toxic byproducts of lipid peroxidation.

Lipid toxicity

The lipoapoptosis mechanism described above has been observed in cardiomyocytes of ZDF rats and in

transgenic mice in which lipotoxic heart disease was induced through the over-expression of long chain fatty acyl-CoA synthetase and the protein transporting fatty acids within cardiomyocytes. Subsequent research has revealed that excessive lipid accumulation may also activate apoptosis by directly inhibiting the mitochondrial respiratory chain and inhibiting the activity of the Akt kinase. Inhibition of the Akt kinase by ceramide is also one of the mechanisms linking excessive lipid accumulation with the inhibition of the insulin signal transduction pathway. It is worth noting that inhibiting ceramide synthesis and lipid peroxidation completely inhibits cardiomyocyte apoptosis and returns normal contractile heart function in ZDF rats. The same effect was observed after the administration of troglitazone, a drug that reduces intracellular lipid accumulation and increases sensitivity to insulin. A growing amount of data indicates that excessive accumulation of fat in cardiomyocytes and the toxic effects of lipids may form the basis of pathogenesis of heart failure. The latest studies conducted using magnetic resonances spectroscopy confirm a significant correlation between accumulation of lipids in the heart muscle and left ventricle dysfunction in obese people.

Regardless of diet

Stearoyl-CoA desaturase (SCD) is one of the main enzymes involved in monounsaturated fatty acid synthesis. The enzyme catalyzes the introduction of a double bond between the 9th and 10th carbon atoms in palmitic or stearic acid, leading to the formation of palmitoleic or oleic acid, respectively. Research carried out using SCD1-/- mice shows that the animals do not accumulate fat regardless of their diet (including high in fats and carbohydrates), even though they consume 25% more on average than SCD1+/+ mice. The animals are also resistant to obesity caused by leptin deficiency. Further research conducted at the Nencki Institute of Experimental Biology, Polish Academy of Sciences, shows that SCD also plays an important role in the regulation of cardiac muscle metabolism. Two isoforms of the SCD gene are expressed in the heart (SCD1 and SCD4); SCD4 is unique to this organ. The research shows that introducing a mutation that fully silences the SCD1 gene (gene knockout) leads to increased utilization of glucose as an energy substrate with concurrent reduction of the rate of utilization of fatty acids in cardiac muscle. ECG studies have shown that this does not cause arrhythmia. Subsequent experiments have shown that knocking out the SCD1 gene in ob/ob mice leads to a significant reduction of lipid accumulation in the heart, reduced cardiomyocyte apoptosis, and a significant improvement of left ventricle function. The changes are accompanied by a reduction in fatty acid transport into the cells, inhibition of expression of genes responsible for lipid synthesis, and reduced expression of genes linked with lipid oxidation. The reduction of intracellular fatty acid levels together with the accompanying reduction of expression of oxidative genes leads to a reduction in the rate of fatty acid oxidation, which itself may have a positive effect on heart function. However, knocking out the SCD1 gene also leads to inhibited expression of the gene coding for serine palmitoyltransferase, an enzyme regulating *de novo* synthesis and ceramide accumulation. A reduction in ceramide content leads to reduced cardiomyocyte apoptosis by increasing the expression of the Bcl2 antiapoptotic factor and inhibiting nitric oxide synthase activity.

Intracellular pathway therapy

It appears that reducing the accumulation of intracellular lipids and inhibiting cardiomyocyte apoptosis are the main mechanisms leading to improved left ventricle function linked with knocking out the SCD1 gene. The results show that a therapy targeted at intracellular pathways that regulate lipid metabolism in cardiomyocytes helps recover their normal contractile function, and could be successfully used in the treatment of obesity-related heart dysfunction. ■

Further reading:

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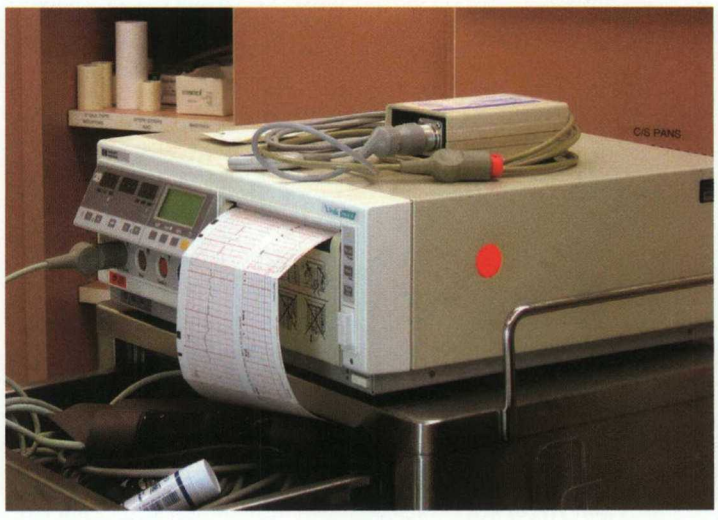

ECG studies carried out in obese rat and mouse models have shown a significant reduction in left ventricular contractility, caused by apoptosis of cardiomyocytes resulting from lipid management disorders