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A natural product derived from fatty acids found in nuts and seeds reduce obesity

Obesity is a major worldwide epidemic. In the US, one third of the population is overweight, another third is obese. There are many complications of obesity, including metabolic syndrome, diabetes, heart disease, fatty liver, high blood pressure, cancer and arthritis. Although the cause of obesity includes a genetic component, the most important contributing factor is that we eat more calories than the body use up. Metabolic syndrome in itself is not a disease, it is a group of risk factors; high blood sugar, high blood pressure, unhealthy cholesterol levels, abdominal fat deposition and inflammation. We have all seen people with very large waist circumference due to excess abdominal fat (apple-shaped body). Some people have more subcutaneous fat, which is a less dangerous form of fat, and the associated body composition where the waist is narrower than the hip is referred to as the pear shape. People with a huge belly are the most at risk for the development of severe vascular disease, including stroke, heart attack and peripheral vascular disease.

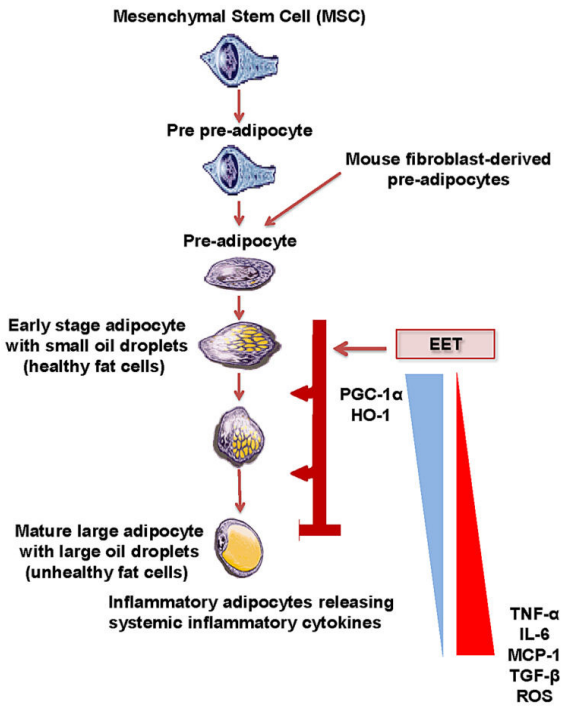

Fig. 1. Schematic presentation of the possible mechanism by which EETs help to maintain healthy fat cells and control and prevent the development of large unhealthy fat cells. Healthy fat cells have increased expression of proteins and other molecules that favor normal cell metabolism and low level inflammation. Unhealthy fat cells have reduced expression of protective proteins and molecules and secrete higher levels of proteins and molecules that drive inflammation, both locally and systemically (the whole body).

The excess fat can also be stored in organs, such as the liver, kidneys and heart. Fatty liver is a condition that in severe cases can cause inflammation of the liver, resulting in cirrhosis. The excess abdominal fat secretes products that cause inflammation and that create the onset of cardiovascular disease. Moreover, this excess fat is what causes the abnormal fasting blood sugar levels, high blood pressure and abnormal lipid profile.

We tried to solve this medical problem in the laboratory. We focused on the epoxyeicosatrienoic acids (EETs) and their ability to upregulate the heme oxygenase system; the body's first line of defense against the inflammatory attack created by excessive abdominal fat. EETs are endogenous fatty acids that are derived from arachidonic acid, which in turn is derived from linoleic acid, commonly found in nuts, fatty seeds from e.g., flax, hemp, poppy and sesame and their derived vegetable oils; comprising over half (by weight) of poppy and sunflower seeds, safflower, corn and soybean oils. Linoleic acid is essential, meaning that the body cannot produce it and therefore must be ingested through foods. Increased fat mass is dependent on the development of new fat cells from existing stem cells, e.g., bone marrow-derived mesenchymal stem cells, and mouse fibroblast-derived pre-adipocytes (Fig. 1).

We found that EET-treatment of high fat diet fed obese mice led to weight loss and increased metabolic rate as determined by increased mitochondrial content and viability and increased total body oxygen consumption. Moreover, EET-treatment of pre-adipocyte stem cells cultured in adipogenic medium *in vitro* developed into smaller and healthier fat cells. EET-treatment of both mice and cells increased levels of a protein called PGC-1α that in turn helped to increase the levels of heme oxygenase. The treatment with EETs also lowered the levels of inflammatory proteins, such as tumor necrosis factor α (TNF-α), inteleukin 6 (IL-6), monocyte chemoattractant protein 1 (MCP-1), and transforming growth factor beta (TGF-β). At the same time these healthier fat cells are more resistant to oxidative stress (ROS) due to the higher levels of antioxidants, including heme oxygenase, that also contribute to decreased inflammation. However, the treatment of mice and cells with EETs had no beneficial effect when the actions of the PGC-1α protein and the induction of heme oxygenase were blocked. This means that the beneficial effects of EETs are dependent on both PGC-1α and heme oxygenase levels.

To summarize, this study shows that the beneficial effect of including linoleic acid in the diet is dependent on the actions of its metabolic products and their induction of the heme oxygenase system.

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