Study establishes a timeline of obesity

September 28 2017

Licio Augusto Veloso during FAPESP Week Nebraska-Texas. Credit: Karina Toledo/ Agencia FAPESP

When investigating the factors associated with the growing epidemic of obesity in the world over the last decade, scientists have identified two

events that greatly contribute to weight gain. One is an alteration in the profile of bacteria that make up the intestinal flora. Studies published from 2005 to 2007 showed that obese people generally present a set of microorganisms that stimulate the absorption of nutrients from food. That means an apple can be more fattening to an obese person than to a lean person. But we still do not know for sure whether this is the cause or the consequence of being overweight.

Another important change is the death of a group of neurons found in the hypothalamus. Known as POMC neurons, these cells function as nutrient sensors that tell the body that it is time to stop eating and that there is enough energy to expend. Studies have shown that after the loss of these sensors, individuals increasingly feel the need to ingest foods rich in fat and sugar. Conversely, their metabolism slows down, and they store most of the energy provided by the unbalanced diet.

"What comes first? The change in the patient's eating patterns caused by an error in the brain system that controls hunger? Or a change in the intestinal microbiome? Our most recent data suggest that the hypothalamus is damaged well before changes occur in the intestine," said Licio Augusto Velloso at the University of Campinas.

In a talk given in Lincoln, Nebraska, on September 19, Velloso presented the findings of a study carried out at the School of Medical Sciences (FCM) at UNICAMP during the postdoctoral studies of Daniela Razolli. The group conducted a time-series analysis of the tissues of mice fed a diet rich in saturated fats. The study lasted a total of four months, enough time for the animal to become obese. At various points throughout the experiment, a portion of the colony was sacrificed so that the researchers could analyze the brains and intestines.

"We began to detect hypothalamic alterations on the very first day of the obesogenic diet. But it took about two to three weeks for changes in the

intestinal microbiota to appear. This is a relatively big time difference, considering that they are mice," Velloso explained.

In previous studies, the group had described how damage to the POMC neurons occurred. The molecules of saturated fat are absorbed by the intestine, enter the bloodstream and reach the brain together with the other nutrients in the food. In the central nervous system, defensive cells known as microglia identify the excess fat as a threat to the neurons and begins to produce inflammatory molecules as if it were combating a pathogen.

"Initially, the inflammation undermines the proper functioning of the hypothalamic neurons. If this goes on for too long, the cells end up dying. This is probably the reason why individuals who have been obese for a long time have trouble losing weight and keeping weight off after various treatments. These individuals are simply no longer able to achieve balance in the flow of energy in the body," Velloso said.

As the experiment with mice showed, the neuronal damage starts well before the individual begins to gain weight, but can be reversed early in the process. If the inadequate diet persists, said Velloso, injury to the neuron becomes irreversible. "If an individual has a meal rich in saturated fats, but then spends several days ingesting a high-fiber diet supplemented by vegetables, the inflammation in the hypothalamus diminishes and the neurons recover. If the obesogenic diet becomes more frequent, it will lead to a gradual increase in the inflammatory process," the researcher said.

An unbalanced diet changes a series of metabolic parameters promoting the development of diabetes and hypertension. In this context, said Velloso, the change in intestinal microbiota emerges, which in turn aggravates obesity and associated diseases. According to Velloso, studies by other groups have shown that a diet rich in simple carbohydrates such

as those in sugar and white flour can also increase lipid levels in the blood and indirectly promote inflammation in the hypothalamus.

"When comparing the two types of diets, however, the researchers concluded that the results are worse when there is excessive consumption of saturated fat," Velloso said. The leading source of saturated fat in the human diet are foods of animal origin such as fatty meats, butter and dairy products. Saturated fat is also found in oil and by-products of coconut and in palm oil as well as in various processed foods such as cookies, ice cream, cakes and pies.

According to Velloso, recent studies suggest that it is possible to promote neurogenesis in the hypothalamus—in other words, to stimulate the emergence of new POMC neurons in an attempt to fight obesity. But for now, this has only been tested in experiments with laboratory rodents. Much more research is needed to understand how the process of cell differentiation can be controlled.

"We are currently at the stage where we understand how the neural precursor cells in the brain function. We need to determine which factors have to be activated to trigger the process of neurogenesis. It is a first step, but may end up being a therapeutic solution to obesity in the future," Velloso said.

Shortly before the presentation by Velloso, U.S. researcher Andrew Benson gave an overview of the Nebraska Food for Health Center, established nearly a year ago for the purpose of developing foods with proven health benefits, particularly those that affect the intestinal microbiome. "Our food production system is currently concerned about such things as reducing costs, increasing productivity, and using resources more efficiently. But health concerns appear only with respect to safety. In other words, the system is more concerned about not killing people than it is about promoting health. We need a new paradigm,"

Benson said.

The idea, according to the researcher, is to study the genetic diversity of local crops, particularly soybeans, beans and other grains, in order to identify components found in these foods that are capable of beneficially influencing the profile of intestinal bacteria. In the future, the most promising compounds may be isolated and added to other types of processed foods.

In Benson's view, this approach can fight metabolic, autoimmune and cardiovascular diseases, as well as cancer, intestinal bowel diseases and even neurological and lung diseases. "We have a plan for the next 10 years. In the first five years, we will focus on our local crops and diseases. Then, in the next five, we will approach the problem in a more comprehensive manner, and for that will need international partners," he emphasized.

Provided by FAPESP