High-fat, high-carbohydrate diets affect your brain, not just your physical appearance

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Much research has pointed to how an unhealthy diet correlates to obesity, but has not explored how diet can bring about neurological changes in the brain. A recent Yale study has discovered that high-fat diets contribute to irregularities in the hypothalamus region of the brain, which regulates body weight homeostasis and metabolism.

Led by Sabrina Diano, the Richard Sackler Family Professor of Cellular & Molecular Physiology and professor of neuroscience and comparative medicine, the study evaluated how the consumption of a high-fat diet—specifically diets that include high amounts of fats and carbohydrates—stimulates hypothalamic inflammation, a physiological response to obesity and malnutrition.

The researchers reaffirmed that inflammation occurs in the hypothalamus as early as three days after consumption of a high-fat diet, even before the body begins to display signs of obesity. "We were intrigued by the fact that these are very fast changes that occur even before the body weight changes, and we wanted to understand the underlying cellular mechanism," said Diano who is also a member of the Yale Program in Integrative Cell Signaling and Neurobiology of Metabolism.

The researchers observed hypothalamic inflammation in animals on a high fat diet and discovered that changes in physical structure were occurring among the microglial cells of animals. These cells act as the first line of defense in the central nervous system that regulate inflammation. Diano's lab found that the activation of the microglia was due to changes in their mitochondria, organelles that help our bodies derive energy from the food we consume. The mitochondria were substantially smaller in the animals on a high-fat diet. The mitochondria's change in size was due to a protein, Uncoupling Protein 2 (UCP2), which regulates the mitochondria's energy utilization, affecting the hypothalamus' control of energy and glucose homeostasis.

The UCP2-mediated activation of microglia affected neurons in the brain that, when receiving an inflammatory signal due to the high fat diet, stimulated the animals in the high-fat diet group to eat more and become obese. However, when this mechanism was blocked by removing the UCP2 protein from microglia, animals exposed to a high fat diet ate less and were resistant to gain weight.

The study not only illustrates how high-fat diets affect us physically, but conveys how an unhealthy diet can alter our food intake neurologically. "There are specific brain mechanisms that get activated when we expose ourselves to specific type of foods. This is a mechanism that may be important from an evolutionary point of view. However, when food rich in fat and carbs is constantly available it is detrimental."

Diano's long-standing goal is to understand the physiological mechanisms that regulate how much food we consume, and she continues to perform research on how activated microglia can affect various diseases in the brain, including Alzheimer's

disease, a neurological disorder that is associated with changes in the brain's microglial cells and has been shown to have higher incidence among obese individuals.

The study was published in *Cell Metabolism*.

More information: Jung Dae Kim et al. Microglial UCP2 Mediates Inflammation and Obesity Induced by High-Fat Feeding, *Cell Metabolism* (2019). DOI: 10.1016/j.cmet.2019.08.010