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Study shows how 'body clock' dysregulation underlies obesity, more

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A team of Texas A&M University System scientists have investigated how "body clock dysregulation" might affect obesity-related metabolic disorders.

The team was led by Dr. Chaodong Wu, associate professor in the department of nutrition and food sciences of Texas A&M's College of Agriculture and Life Sciences, and Dr. David Earnest, professor in the department of neuroscience and experimental therapeutics, Texas A&M Health Science Center.

Study results were published recently on the *Journal of Biological Chemistry* website.

"Animal sleeping and eating patterns, including those of humans, are subject to a circadian rhythmicity," Earnest said. "And previous studies have shown an association between the dysregulation of circadian or body clock rhythms and some metabolic disorders."

Wu said circadian clocks in peripheral tissues and cells drive daily rhythms and coordinate many physiological processes, including inflammation and metabolism.

"And recent scientific observations suggest that disruption of circadian clock regulation plays a key role in the development of metabolic diseases, including obesity and diabetes," he noted.

He said this study affirms that eating unhealthy foods causes health problems and that it's much worse to eat unhealthy foods at the wrong time. It also indicates that "time-based treatment may provide better management of metabolic diseases.

"To promote human health, we need not only to eat healthy foods, but also more importantly to keep a healthy lifestyle, which includes avoiding sleeping late and eating at night," he said.

Wu and Earnest said while previous studies using mice with genetic mutation of the removal of core clock genes has indicated that specific disruption of circadian clock function alters metabolism or produces obesity, the mechanism remained unknown. As key components of inflammation in obesity, macrophages, which are immune cells, contain cell-autonomous circadian clocks that have been shown to gate inflammatory responses.

"Our hypothesis was that overnutrition causes circadian clock dysregulation, which induces pro-inflammatory activity in adipose tissue. This then worsens inflammation and fat deposition, leading to systematic insulin resistance," Wu said.

To test the hypothesis, the team conducted experiments with "reporter mice" in which the circadian rhythmicity of various types of cells could be monitored by looking at their reporter activity. Accordingly, the reporter mice were put on a 12-hour light-dark cycle and were fed a high-fat diet. Additional reporter mice were fed a low-fat diet and served as controls. In this set of experiments, the team was able to characterize the effects of a high-fat diet on circadian clock rhythmicity and inflammatory responses in immune cells, or macrophages.

To further define a unique role for circadian clock dysregulation in metabolic disorders, the team conducted "bone marrow transplantation"

experiments, through which the rhythmicity of circadian clocks was disrupted only in a specific type of immune cells. After high-fat diet feeding, the transplanted mice were used for collection of blood and tissue samples. A number of physiological and immunological assays also were performed on the mice.

Earnest said results showed that during obesity, that is when mice were fed a high-fat diet, the rhythmicity of circadian clocks in immune cells of fat tissue is dysregulated by a prolonged rhythmic period. This is, in turn, is linked to increased accumulation of immune cells in fat tissue and decreased whole-body insulin sensitivity.

"Animals on a high-fat diet display metabolic problems associated with obesity," Earnest said. "The problems are worsened in animals whose circadian clocks in immune cells are disrupted."

Earnest and Wu said the study will help those involved in human health and nutrition better understand the underlying mechanisms related to obesity and diabetes.

More information: Paper: www.jbc.org/content/early/2014 … 4/25/jbc.M113.539601

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