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Insulin Directly Regulates the Circadian Clock in Adipose Tissue

Eating at the wrong time of day disrupts our circadian rhythm and increases the risk of obesity and type 2 diabetes. The team led by PD Dr. Olga Ramich of DIfE, Professor Achim Kramer and Professor Andreas F. H. Pfeiffer of Charité – Universitätsmedizin Berlin provides initial explanations for this phenomenon in a new study. The researchers have shown for the first time in human samples that insulin can influence the circadian clock of adipose tissue. The results were published in the journal Diabetes.

Synchronized from head to toe

Our internal clock regulates almost all physiological processes, for example metabolism, blood pressure and body temperature. In addition to the central internal clock, which is located in the suprachiasmatic nucleus of the hypothalamus, there are many subordinate clocks that are found in every organ, tissue and cell of the body. Circadian rhythms are based on a close interplay of so-called clock genes that generate a 24-hour rhythm via interlocking feedback loops. New studies show that meal timing and food composition can alter the circadian rhythm of various tissues. Metabolically active, insulin-sensitive tissues, such as liver and adipose tissue, are particularly affected. In addition, the timing of food intake that is out of sync with the internal clock increases the risk of obesity and metabolic diseases such as metabolic syndrome and type 2 diabetes. However, so far little is known about the underlying mechanisms.

Insulin changes clock gene expression

For the current study, the research team led by Ramich, Kramer and Pfeiffer investigated the influence of increased postprandial insulin levels on the circadian rhythm of adipose tissue and which molecular mechanisms play a role in this. For this purpose, they analyzed adipose tissue samples from 17 obese, non-diabetic men taken before and four hours after the so-called hyperinsulinemic-euglycemic clamp*. "This method is usually used to determine insulin sensitivity. But it was also ideal for our research question because it allowed us to study the pure effects of insulin on adipose tissue in humans in vivo," said Ramich, who leads the research group Molecular Nutritional Medicine at DIfE. The scientists isolated the genetic material from the adipose tissue samples and determined the expression of various genes. Compared to the control group, which had received a saline solution instead of insulin, there was a marked change in the expression of clock genes, suggesting an insulin-dependent regulation of the internal clock.

Circadian rhythms made visible

To elucidate the molecular mechanisms responsible for this regulation, the researchers used human and animal adipocytes that had been genetically modified in culture or isolated from a genetically modified mouse model. A luciferase** gene was inserted into these cells and fused to a segment of the Per2 gene. Per2 is one of the key genes of the molecular clockwork. Thanks to luciferase, these cells generate light in response to Per2 expression, which allowed the scientists to observe the circadian rhythms of Per2 in real time over several days. "We found that insulin causes a rapid and transient increase in Per2 expression, altering the overall clock rhythm," said Dr. Neta Tuvia, who shares first authorship of the study with Dr. Olga Ramich.

Key gene segments identified

In molecular biology experiments, the researchers then identified those segments of the Per2 gene that are crucial for the insulin effect. Piece by piece, they trimmed the promoter – the DNA segment that controls the expression of a gene – and found that the region between 64 and 43 base pairs plays an essential role. "Our findings show for the first time the way in which mistimed eating can disturb our circadian rhythms and cause negative metabolic changes," said Ramich, summarizing the results. "This may also explain why eating at night has a particularly unfavorable effect on metabolism." The researchers assume that the mechanisms leading to the eating-related change in the internal clock are even more complex and that other hormones and metabolites are involved. This remains to be investigated in future studies.

Background information

* Hyperinsulinemic-euglycemic clamp

This method is considered the gold standard for determining insulin sensitivity. A defined amount of insulin is infused into a person and glucose is gradually added until a normal fasting blood glucose level is achieved. The more glucose that needs to be administered, the higher the insulin sensitivity of the person. The less glucose needed, the greater the insulin resistance.

** Luciferase

Luciferases are enzymes that can produce light via a catalyzed reaction. They are found in various organisms, e.g. in fireflies, deep-sea fish and fungi. Luciferases have a wide range of applications in biotechnology and are often used as markers.

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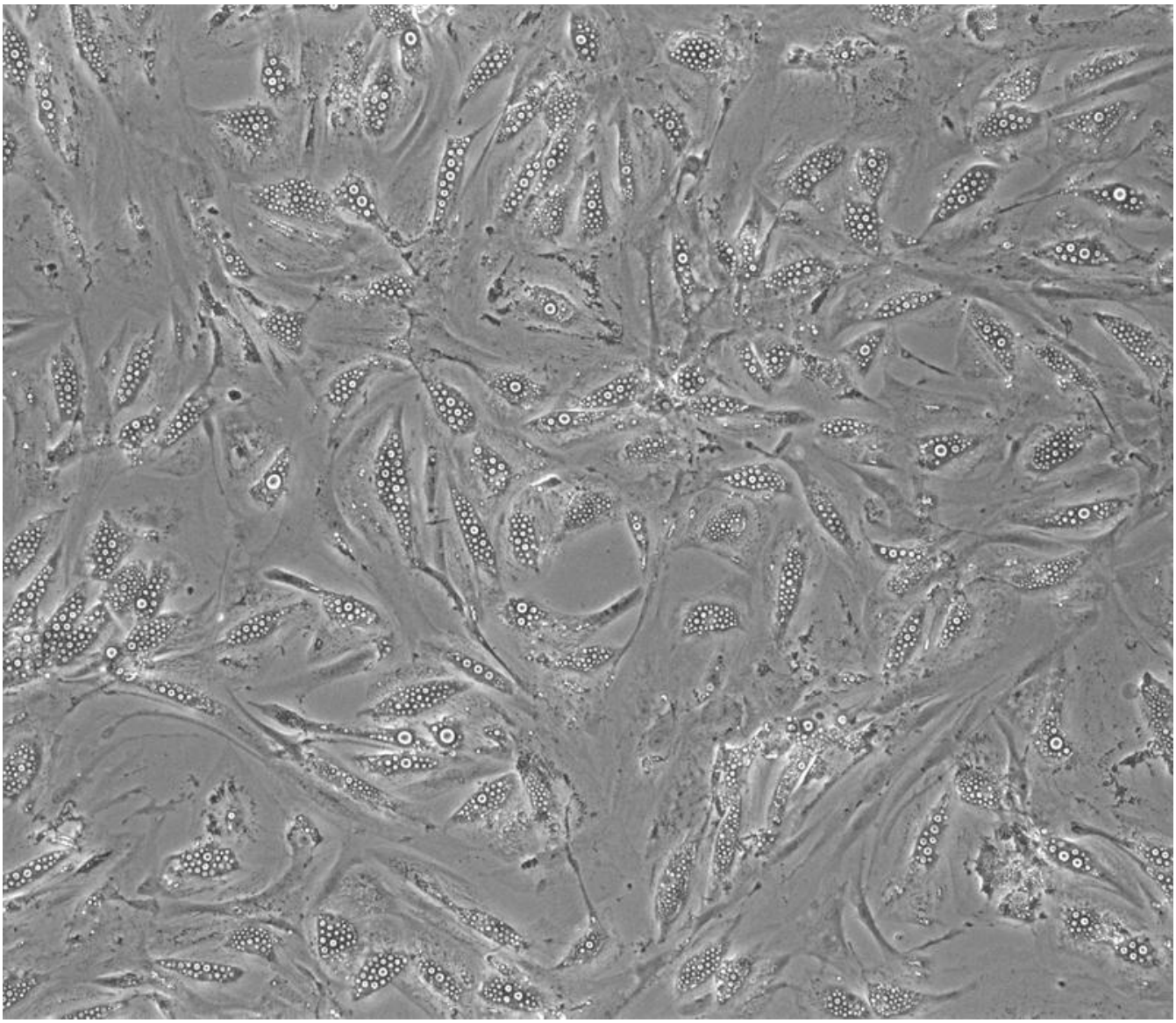
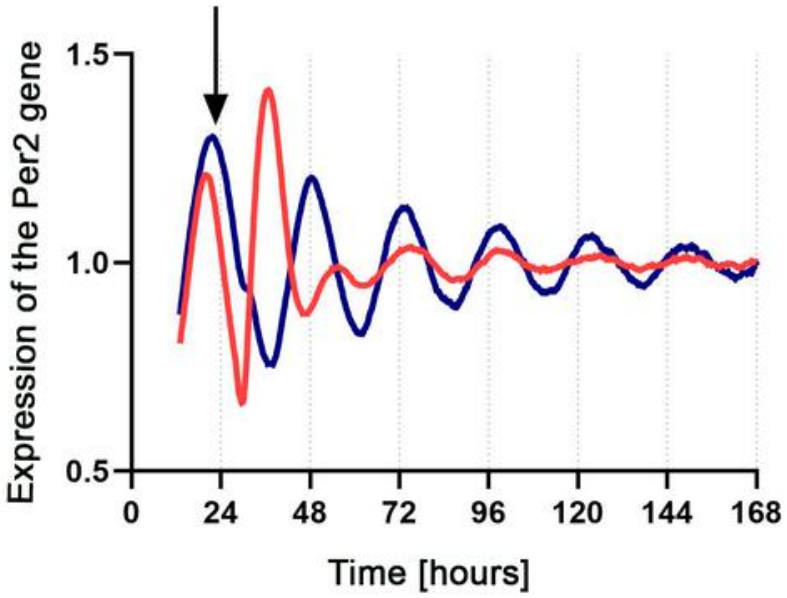


Microscopic image of human adipocytes in which lipid droplets (white) accumulate.
DIfE



Circadian rhythms of the Per2 gene in human adipocytes without (blue line) and with insulin stimulation (red line).
The black arrow indicates the time of insulin stimulation.

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