Muscle Clocks and Diabetes

Obesity

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The number of people suffering from type 2 diabetes mellitus (T2DM) is increasing rapidly. T2DM increases the risk of cardiovascular disease and other complications and reduces life expectancy by 5 to 10 years, posing a major burden on our health care system. Because obesity is the strongest risk factor for the development of type 2 diabetes, a positive energy balance leading to weight gain and insulin resistance has to be involved in the etiology of T2DM. Similarly, disturbances in glucose, protein, and fat metabolism in major insulin-responsive tissues such as muscle, liver, and heart, together with reduced beta-cell function, play an important role in the development of insulin resistance and T2DM. In turn, these pathways are markedly influenced by environmental factors that affect energy expenditure and energy intake, such as physical (in)activity and food intake.

A still undervalued environmental factor contributing to diabetes that is gaining rapid (scientific) interest is our modern 24/7 society. Indeed, one of the major breakthroughs of the past few decades in our understanding of energy homeostasis has been the identification of a reciprocal control between circadian rhythmicity and cellular metabolism. Circadian rhythmicity is a fundamental endogenous process of almost every organism living on Earth. In mammals, the temporal organization of metabolism, physiology, and behavior around the 24-hour light/dark cycle is controlled by a network of multiple tissue clocks, synchronized by a brain master clock. The intrinsic rhythmicity of all these clocks is generated by a molecular clock mechanism composed of a negative feedback loop mediated via the proteins period and cryptochrome that represses circadian locomotor output cycles kaput/Brain and muscle Arnt-like protein-1-mediated gene transactivation.

In April 2019, an international scientific meeting on "Muscle Clocks and Diabetes" was organized in Amsterdam, The Netherlands. This special issue of *Obesity* compiles several perspective papers, reviews, and original research articles that were presented at the meeting and that feature recent advancements in the mechanisms linking circadian clocks in skeletal muscle with energy metabolism as well as the pathophysiological implications of these interactions for metabolic health.

The circadian rhythmicity of the brain master clock is synchronized with the exact 24-hour rhythm of the environment, mainly by ambient light perceived by the retina, while the secondary clocks in peripheral organs and tissues can be reset by meal timing and exercise. In experimental animals, modification of clock-controlled genes as well as desynchronized daily rhythms results in insulin resistance and obesity. The relevance of such desynchronization in humans is underscored by the increased risk of obesity and T2DM in night shift workers. Similarly, studies in which an experimental circadian misalignment is imposed lead to striking disturbances in glucose homeostasis and insulin resistance. Given that nowadays most of the population does not restrict food intake and activity to only daytime hours, the impact of circadian disturbances on metabolism and human health needs to be better understood. Studies assessing the functional links between circadian desynchronization and overall health are needed.

So far, physical activity and calorie restriction are considered the best strategies to prevent T2DM. A common characteristic of both strategies is that they act through positive effects on skeletal muscle energy homeostasis, including mitochondrial capacity. Interestingly, novel data suggest that skeletal muscle metabolism is also under the control of the circadian timing system. So far, only a few studies have investigated the relation between (disturbance of) the circadian timing system, skeletal muscle energy metabolism, and insulin sensitivity. Yet such information is important, as it may reveal further insight in the development of insulin resistance and T2DM and therefore provide important information to optimize therapeutic strategies to combat the disease. For example, the appropriate circadian timing of physical activity bouts or combining exercise and intermittent fasting strategies may improve metabolic health in individuals at risk for metabolic diseases. Indeed, novel strategies such as time-restricted feeding and timing of exercise have shown initial beneficial health effects and need further investigation.

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