Role of clock genes in insulin secretion

Circadian locomotor output cycles kaput (CLOCK) and brain and muscle aryl hydrocarbon receptor nuclear translocator-like protein 1 (BMAL1) are master clock genes that regulate circadian rhythm in the hypothalamus and peripheral tissues in mammals; and control not only sleep cycle, but also many other physiological functions, such as body temperature, heart rate and hormone secretion. CLOCK and BMAL1 protein form a heterodimer and bind to enhancer box (E-box) elements located upstream of circadian rhythm-related genes, which are period (PER) and cryptochrome (CRY), and non-circadian rhythm-related genes, resulting in production of PER, CRY and other non-circadian rhythm-related proteins. In the cytoplasm, PER and CRY protein form a heterodimer that is subsequently translocated into the nucleus and inhibits CLOCK and BMAL1-induced transcriptions. This negative feedback loop is an important part of mammalian circadian rhythm (Figure 1).

Recent studies of CLOCK-mutant and BMAL-knockout mice show that circadian rhythm influences the development of metabolic syndrome. Locomotor activity of CLOCK-mutant mice was higher than that of wild-type mice in the light phase condition, and the feeding pattern of the mutant mice was apparently different from that of wild-type mice. Energy expenditure was decreased and bodyweight was increased in the mutant mice compared with wild-type mice. In contrast, bodyweight and adipose tissue size were significantly decreased in systemic BMAL1-knockout mice compared with wild-type mice. BMAL1-knockout mice had higher plasma triglyceride and low-density lipoprotein cholesterol concentrations compared with wild-type mice. These results show that CLOCK and BMAL1 are involved in lipid metabolism and bodyweight control. However, there was a large difference in phenotype between CLOCK-mutant and BMAL-knockout mice. It is speculated that CLOCK and BMAL1 regulates different non-circadian proteins, which are associated with lipid metabolism and obesity.

Previously, β-cell-specific BMAL1-knockout mice were generated to evaluate the effect of BMAL1 on insulin secretion. Plasma insulin concentrations after intraperitoneal glucose injection were apparently different from that of wild-type mice. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.
contained the active enhancer at which pancreatic transcriptional factor pancreatic and duodenal homeobox 1 bind. Thus, clock genes regulate the genes (Pdx1) that are associated with insulin secretion and production in β-cells.

**DISCLOSURE**
The authors declare no conflict of interest.

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**REFERENCES**


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