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COMMENTARY

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)[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[2]. Energy expenditure was decreased and bodyweight was increased in the mutant mice compared with that in wild-type mice. Furthermore, plasma triglyceride and low-density lipoprotein cholesterol concentrations were decreased in mutant mice. In contrast, bodyweight and adipose tissue size were significantly decreased in systemic BMAL1-knockout mice compared with wild-type mice.[3] 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[4]. Plasma insulin concentrations after intraperitoneal glucose injection were significantly lower in β-cell-specific BMAL1-knockout mice compared with those in wild-type mice, resulting in hyperglycemia. Insulin secretion in response to glucose, adenylyl cyclase activator (forslolin), glucagon-like peptide-1 receptor agonist (exendin-4), cyclic adenosine 3′, 5′-monophosphate (8-bromo-cyclic adenosine 3′, 5′-monophosphate) and hyperdepolarization (KCl) were significantly decreased in the isolated islets of β-cell-specific BMAL1-knockout mice compared with wild-type mice. These results show that BMAL1 is also involved in insulin secretion. However, the detailed mechanism of BMAL1-mediated regulation of insulin secretion from pancreatic β-cells is unclear. Perelis *et al.*[5] clearly showed the regulatory role of BMAL1 in insulin secretion by genome-wide analysis of isolated islets. They generated tamoxifen-induced β-cell-specific BMAL1-knockout mice, and showed that acquired BMAL1 deficiency in β-cells decreases insulin secretion in response to glucose, forskolin, 8-bromo-cyclic adenosine 3′, 5′-monophosphate and KCl. Genomic-wide analysis using ribonucleic acid sequence suggested reduction of not only circadian rhythm-related genes, but also genes associated with transport and membrane fusion of insulin vesicle in the islets. Additionally, data of chromatin immunoprecipitation-sequence showed that CLOCK and BMAL1 bind at distal regulatory sites of circadian rhythm-related genes in β-cells. This region also

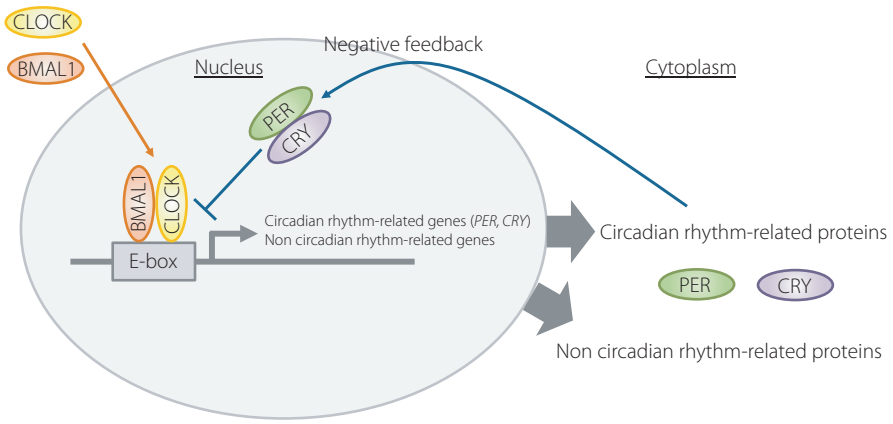

Figure 1 | Molecular mechanism of circadian rhythm. Circadian locomotor output cycles kaput (CLOCK) and brain and muscle aryl hydrocarbon receptor nuclear translocator-like protein 1 (BMAL1) protein form a heterodimer and bind to E-box elements, resulting in induction of period (PER), cryptochrome (CRY) and non-circadian rhythm-related gene transcriptions. In the cytoplasm, PER and CRY protein is subsequently translocated into the nucleus, and inhibits CLOCK and BMAL1-induced transcriptions (negative feedback). E-box, enhancer box.

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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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