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Loss of circadian rhythm of circulating insulin concentration induced by high-fat diet intake is associated with disrupted rhythmic expression of circadian clock genes in the liver

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ABSTRACT

Objective. Peripheral clock genes show a circadian rhythm is correlated with the timing of feeding in peripheral tissues. It was reported that these clock genes are strongly regulated by insulin action and that a high-fat diet (HFD) intake in C57BL/6 J mice for 21 days induced insulin secretion during the dark phase and reduced the circadian rhythm of clock genes. In this study, we examined the circadian expression patterns of these clock genes in insulin-resistant animal models with excess secretion of insulin during the day.

Materials/Methods. We examined whether insulin resistance induced by a HFD intake for 80 days altered blood parameters (glucose and insulin concentrations) and expression of mRNA and proteins encoded by clock and functional genes in the liver using male ICR mice.

Results. Serum insulin concentrations were continuously higher during the day in mice fed a HFD than control mice. Expression of lipogenesis-related genes (*Fas* and *Accβ*) and the transcription factor *Chrebp* peaked at zeitgeber time (ZT)24 in the liver of control mice. A HFD intake reduced the expression of these genes at ZT24 and disrupted the circadian rhythm. Expression of *Bmal1* and *Clock*, transcription factors that compose the core feedback loop, showed circadian variation and were synchronously associated with *Fas* gene expression in control mice, but not in those fed a HFD.

Conclusions. These results indicate that the disruption of the circadian rhythm of insulin secretion by HFD intake is closely associated with the disappearance of circadian expression of lipogenic and clock genes in the liver of mice.

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Abbreviations: ACC, acetyl-CoA carboxylase; BMAL1, brain and muscle *Arnt*-like protein-1; ChREBP, carbohydrate-responsive element-binding protein; CLOCK, circadian locomotor output cycles kaput; CRY, CRYPTOCHROME; FAS, fatty acid synthase; PER, PERIOD; Rev-erb, nuclear receptor subfamily 1 group D; ROR, retinoic acid receptor-related orphan receptor.

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1. Introduction

Circadian rhythmicity is the ability of most organisms to adapt to the environment, mainly the 24-h cyclic pattern of light and the daily pattern of food intake. Recent advances suggest that circadian rhythms are controlled by a molecular timer that consists of a set of genes related to transcriptional regulators known as "clock genes." Among these clock genes, a heterodimer of BMAL1 and CLOCK transcription factors drives the "core loop" of the clock genes. The BMAL1-CLOCK heterodimer induces the expression of the negative regulators *Per1-3* and *Cry1-2* through binding to a cis-element such as an E-box in the promoter/enhancer region of these genes. Circadian rhythmicity is achieved when the PER-CRY complex represses the transcription of these genes by inhibiting the transport of the BMAL1-CLOCK heterodimer in the nucleus [1,2]. In addition, recent studies demonstrated that the BMAL1-CLOCK heterodimer regulates functional genes in peripheral tissues as well as *Per1-3* and *Cry1-2* [3–5], resulting in each functional gene in each tissue exhibiting circadian rhythmicity according to the 24-h cyclic pattern of light and the daily pattern of food intake.

Circadian rhythmicity is controlled by the central clock in the suprachiasmatic nucleus of the hypothalamus and by the peripheral clock in peripheral tissues such as the liver, adipose tissue, intestine, heart, and kidney [6–9]. The peripheral clock influences physiological phenomena and behaviors including sleep–wake cycles, food intake, physiology of the gastrointestinal tract, and hepatic metabolism [10]. Studies in both rodents and humans suggest that circadian clock regulation is closely associated with energy homeostasis. Circadian disruption caused by shift work in humans is associated with adverse health consequences and the development of obesity and metabolic syndrome [11,12]. In rodents, sleep restriction for 2 weeks caused disrupted gene expression of important regulators of carbohydrate metabolism, such as glucose transporter 2 (*Slc2a2*) and glucose-responsive forkhead box O1 (*Foxo1*) in the liver [13]. Restricted feeding during the light phase changed the phase of clock gene (*Per1*, *Per2*, *Per3*, and *Cry1*) mRNA expression in the liver of mice [14]. This study also showed that adaptation to the restriction occurred more rapidly in the liver than in other organs. Additionally, a recent study demonstrated that phase shifts in the gene expression of clock components and functional genes including *Accα* were observed in the liver of mice that had undergone restricted feeding during the light phase [14]. Furthermore, it was shown that feeding during activity time, i.e., the dark phase in rodents, prevented weight gain and abnormalities of glucose and lipid metabolism in the liver caused by a high fat diet (HFD) intake [15].

Recent studies demonstrated that insulin signals promote the circadian rhythm and associated functional gene expression in peripheral tissues [16–18]. These results indicate that the development of insulin resistance may disrupt the circadian rhythm. Indeed, feeding C57BL/6J mice an HFD for 6 weeks induced hyperglycemia and hyper-insulin secretion during the dark phase (insulin resistance) and reduced the circadian variation of the gene expression of liver *Bmal1* [19]. In general, many animals and humans with insulin resistance had higher blood insulin concentrations during fasting [17,20,21]. However, it is still unclear whether hyperinsulinemia throughout the day alters the circadian expression of clock genes in the liver.

In this study, we examined the effect of HFD for 80 days on the circadian expression of clock and metabolic genes in the liver of ICR mice, which are relatively fertile compared with other strains such as C57BL/6J. ICR mice exhibited severe insulin resistance and hyperinsulinemia but less hyperglycemia when fed HFD [22].

2. Materials and Methods

2.1. Animals

Male ICR mice (Japan SLC, Hamamatsu, Japan) were maintained at a stable temperature (22 ± 2 °C) and humidity (55 ± 5%) under a 12-h light/dark cycle (lights on 07:00–19:00, where zeitgeber time (ZT) 0 and ZT12 indicate the times lights were switched on and off, respectively). Six-week-old ICR mice were divided into two groups and received an HFD or a low-fat diet (control), as summarized in Table 1, for 80 days. Each group was sacrificed by decapitation and tissues were collected at ZT4, 8, 12, 16, 20, and 24 (0 = beginning of lights on). The experimental procedures used in the present study conformed to the guidelines of the Animal Usage Committee of the University of Shizuoka.

2.2. Parameters

Serum glucose and insulin concentrations were measured using the Glucose C-II-Test Wako (Wako Pure Chemical Industries, Osaka, Japan) and REBISU Insulin Mouse ELISA Kit (Shibayagi, Gunma, Japan), respectively.

2.3. RNA Analysis

Total RNA was extracted from the liver using the acidified guanidine thiocyanate method as described by Chomczynski and Sacchi [23]. Total RNA was subjected to reverse transcrip-

Table 1 – Dietary composition of HFD and control.

	HFD	Control
g/kg		
α-Corn starch	99.5	599.5
Sucrose	200	0
Lard	200	0
Safflower oil	200	100
Casein	200	200
AIN93-mineral mix	35	35
AIN93-vitamin mix	10	10
Choline bitartrate	2.5	2.5
L-Cystine	3	3
Cellulose	50	50
Energy (%)		
Carbohydrate	21.4	58.4
Protein	14.3	19.6
Fat	64.2	21.9

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