A CRY for help to fight fat

Oren Froy*

Institute of Biochemistry, Food Science and Nutrition, Robert H. Smith Faculty of Agriculture, Food and Environment, The Hebrew University of Jerusalem, P.O. Box 12, Rehovot 76100, Israel

*Corresponding author:
Oren Froy
Phone: 972-8-948-9746
Fax: 972-8-936-3208
E-mail: oren.froy@mail.huji.ac.il

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Abstract

This is an editorial summarizing recent new developments in the role of the CRY proteins, key components of the circadian clock, in diet-induced obesity and insulin resistance. Understanding the role of the circadian clock or its components in these pathologies may pave the way to novel therapeutic approaches.

Keywords: clock; obesity; CRY; metabolism; circadian rhythms
Obesity has become a serious and growing public health problem (27). Attempts to develop new therapeutic strategies have mostly focused on energy expenditure and caloric intake. Recent studies link energy homeostasis to the circadian clock at the behavioral, physiological, and molecular levels (7, 17, 25). In fact, most aspects of physiology, including sleep-wake cycles, cardiovascular activity, endocrine system, body temperature, renal activity, gastrointestinal tract motility, and metabolism, are influenced by the circadian clock (19).

The circadian clock is a cellular mechanism of gene transcription, translation and posttranslational modifications (23). The mechanism itself exists in both the central clock in the suprachiasmatic nuclei (SCN) and peripheral tissues. Generation of circadian rhythms is achieved by the co-expression of specific clock proteins that serve as transcription factors. The core clock mechanism includes the transcription factor CLOCK, which dimerizes with BMAL1 to activate transcription upon binding to enhancer elements (10). CLOCK:BMAL1 heterodimer mediates transcription of a large number of genes including the Period and Cryochrome genes (Pers and Crys). The PERs (PER1, PER2, and PER3) and CRYs (CRY1 and CRY2) proteins operate as negative regulators (8, 20); they oligomerize, translocate to the nucleus and inhibit CLOCK:BMAL1-mediated transcription.

The expression and/or activity of certain enzymes and transport systems (13) involved in the various metabolic pathways, such as cholesterol metabolism, amino acid regulation, drug and toxin metabolism, the citric acid cycle, and glycogen and glucose metabolism, exhibit circadian expression (7, 9). It has been shown that disruption of circadian expression leads to metabolic disorders. However, the most compelling linkage between metabolic disorders and the circadian clock is demonstrated in the phenotypes of clock gene mutants and knockouts. For example, Bmal1-/- knockout mice and Clock mutant mice, exhibit suppressed diurnal variations in glucose and triglycerides as well
as abolished gluconeogenesis (15, 21). In addition, Per2<sup>−/−</sup> mice display altered lipid metabolism with a drastic reduction of total triglycerides and non-esterified fatty acids (11). However, these phenotypes are strain-, age- and sex-specific. For example, Clock<sup>Δ19</sup> mutant mice have a greatly attenuated diurnal feeding rhythm, are hyperphagic and obese, and develop a metabolic syndrome of hyperleptinemia, hyperlipidemia, hepatic steatosis, and hyperglycemia (25). In contrast, the same mutants crossed either with the ICR or a melatonin-proficient strain are not obese (15, 18). Another example is the Per2 knockout. Whereas Per2<sup>−/−</sup> male mice are considerably heavier during the preadolescence period (postnatal day [pnd] 23–35), during adolescence (pnd 36–48), Per2<sup>−/−</sup> animals slow down their growth rate until approximately the adult age (pnd >61), at which time they become progressively and significantly lighter than wild type (WT) littermates (11). However, regardless of the reported differences, the common denominator is altered metabolism, reiterating the role of the circadian clock in energy homeostasis.

Cry1<sup>−/−</sup>Cry2<sup>−/−</sup> mice lack all rhythmicity in constant darkness, but maintain almost normal rhythmicity under normal light/dark cycle (26). However, the circadian rhythmicity of some clock-controlled system, such as oxygen consumption, heart rate, and body temperature are abolished, suggesting hypermetabolism (14). Cry1<sup>−/−</sup>Cry2<sup>−/−</sup> mice show slightly decreased body weight under normal chow conditions (4), due to inappropriate activation of the sympathetic arm of the autonomic nervous system (14). Whereas knockout or mutations in genes encoding the positive loop of the clock, i.e., Clock and Bmal1, result either in a normal or obese phenotype (12, 15, 25), lower than normal body weight has been reported for knockouts in the genes encoding the negative feedback loop, i.e., Crys and Pers (1, 5, 11). Thus, similarly to Cry1<sup>−/−</sup>Cry2<sup>−/−</sup> mice, Per1<sup>Bnd</sup> (5) and Per2<sup>−/−</sup> (11) mice are lighter than WT mice. In this issue Barclay et al (1) found that under a high-fat diet, male Cry1<sup>−/−</sup>Cry2<sup>−/−</sup> mice respond more rapidly than WT males, and gain much more weight despite overall decreased food
intake. Susceptibility to high-fat diet has been shown in Per (6, 29) and Bmal1 (12) knockouts and Clock mutant (25) mice. The high-fat diet may exacerbate the disruption of the daily metabolic rhythms and result in an obese phenotype, as has been shown (2, 3, 16).

In Cry1\(^{-/-}\)Cry2\(^{-/-}\) mice, high-fat diet induced hyperinsulinemia, as a result of potentiated insulin secretion (1). Per2\(^{-/-}\) mice have recently been reported to be hyperinsulinemic and have increased glucose stimulated insulin secretion (31), contrary to what has been reported for Clock\(^{Δ19}\) and Bmal1\(^{-/-}\) mice (17, 22). At the pancreas level, both Clock\(^{Δ19}\) and Bmal1\(^{-/-}\) mice display defective insulin secretion (17, 22). Taken together, it seems that disruption of the negative feedback loop leads to increased insulin secretion, whereas elimination of the positive loop leads to hypoinsulinemia. Surprisingly, Cry1\(^{-/-}\)Cry2\(^{-/-}\) mice showed selective insulin sensitivity in gonadal adipose tissue, correlating with increased lipid uptake, whereas other tissues, such as the liver and muscle exhibited insulin resistance (1). The increased insulin sensitivity and lipid uptake explain the hypertrophy and lipogenesis-inducing genes in adipose tissue. In addition, the disruption of the daily insulin secretion under high-fat diet in this strain leads to overall insulin resistance in other tissues. Thus, in obese clock mutants and knockouts (Clock and Bmal1) on regular chow, hyperglycemia with hypoinsulinemia, insulin resistance and exacerbated obesity under high-fat diet are observed. However, in the lean clock knockouts (Pers and Crys), once obesity ensues as a result of the high-fat diet, the increased insulin secretion leads on the one hand to the accumulation of fat in adipose tissue and on the other to insulin resistance in other tissues. These metabolic changes perpetuate the obese phenotype.

Although disruption of circadian rhythms leads to metabolic disorders, one must bear in mind that some clock proteins have been shown to play a tissue-specific role, in addition to their role as part of the core clock mechanism. For example, recent molecular studies established the involvement of the activity of the positive circadian transcription factor BMAL1 in the control of adipogenesis and lipid
metabolism (12, 24). Thus, the insulin sensitivity in adipose tissue vs. resistance in other tissues in
Cry1−/−Cry2−/− mice, could indicate an additional role for the CRY proteins. CRY proteins have been
recently shown to inhibit the accumulation of cAMP by binding directly to the G(s)α subunit of the G
protein-coupled receptor (GPCR) and, as a result, decrease gluconeogenesis (30). As high cellular
cAMP levels induce insulin secretion (28), this finding may explain the hyperinsulinemia seen in
Cry1−/−Cry2−/− mice.

Taken together, Barclay et al (1) clearly establish a key role for CRY proteins in diet-induced
obesity and insulin sensitivity in adipose tissue, but insulin resistance in other tissues, therein
extending our understanding of the versatility of core clock components and providing alternative
approaches for future therapy of morbid obesity and type 2 diabetes.

Disclosures

No conflicts of interest, financial or otherwise, are declared by the author.

Author contributions

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References


