ACRY FOR HELP TO FIGHT FAT

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OBESITY HAS BECOME A SERIOUS AND GROWING PUBLIC HEALTH PROBLEM (27). ATTEMPTS TO DEVELOP NEW THERAPEUTIC STRATEGIES HAVE FOCUSED MOSTLY 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 COEXPRESSION OF SPECIFIC CLOCK PROTEINS THAT SERVE AS TRANSCRIPTION FACTORS. THE CORE CLOCK MECHANISM INCLUDES THE TRANSCRIPTION FACTOR CLOCK, WHICH DIMERIZES WITH BRAIN AND MUSCLE ARNT-LIKE PROTEIN-1 (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 CRYPTOCHROME GENES (PERS AND CRYs). THE PER (PER1, PER2, AND PER3) AND CRY (CRY1 AND CRY2) PROTEINS OPERATE AS NEGATIVE REGULATORS (8, 20); THEY Oligomerize, Translocate to the Nucleus, and Inhibit CLOCK:BMAL1-MEDIATED TRANSCRIPTION.


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-/- AND BMAL1-/- MICE (17, 22). AT THE PANCREATIC LEVEL, BOTH CLOCK-/- AND BMAL1-/- MICE DISPLAY DEFECTIVE INSULIN SECRETION (17, 22). TOGETHER, THESE DATA SUGGEST THAT 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 LIPOGENESIS INDUCING ADIPOSE TISSUE (25). 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 OBESICLOCK MICE, A SEVERE OBESITY UNDER HIGH-FAT DIET IS OBSERVED. HOWEVER,
in the lean clock knockouts (Pers and Cry1), 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 Gsα subunit of the G protein-coupled receptor 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. Why this phenomenon is evident only under high-fat diet needs to be further investigated.

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.

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REFERENCES