The Fourth Dimension of Nuclear Receptors, Circadian Rhythms, and Metabolism

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Obesity is a major risk factor for insulin resistance and related metabolic disorders including non-alcoholic fatty liver disease (NAFLD). These diseases have a strong genetic basis, yet their rise has been largely fueled by environmental factors including fattening diets, insufficient physical activity, and exposure to light around the clock. Shift work is a risk factor for metabolic diseases, and this is likely due to dyssynchrony between an individual's endogenous circadian clocks and the timing of their sleep, activity, and eating. The molecular clock consists of a network of transcriptional-translational feedback loops. The body's central clock is located in the suprachiasmatic nucleus (SCN) of the hypothalamus, but nearly all peripheral cells possess autonomous clocks which are synchronized by the central clock as well as by environmental zeitgebers, or timekeepers, including light/dark cycles, feeding, and temperature. Circadian transcriptional rhythms of liver metabolism present opportunities for novel chronotherapeutic approaches. The REV-ERB nuclear receptors are transcriptional repressors that act both as components of the endogenous circadian clock and as direct transcriptional regulators of metabolic processes. Studies on tissue-specific functions of REV-ERBs have identified mechanistic principles by which the epigenome modulates circadian gene transcription, and demonstrate that cell-autonomous circadian clocks facilitate homeostatic adaptation to environmental challenges.