Orphan nuclear receptors, molecular clockwork, and the entrainment of peripheral oscillators.

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Abstract
Here we summarize our work on two aspects of circadian timing: the roles of orphan nuclear receptors in the molecular clockwork, and phase entrainment of peripheral oscillators. With reference to the former, studies on cis-acting regulatory elements within the Bmal1 promoter revealed that REV-ERBalpha, an orphan nuclear receptor provides a link between the positive and negative limbs of the molecular oscillator. Specifically, REV-ERBalpha controls the cyclic transcription of Bmal1 and Clock, the positive limb components. In turn, the circadian expression of Rev-Erbalpha itself is driven directly by the molecular oscillator: it is activated by BMAL1 and CLOCK, and repressed by PERIOD1/2 and CRYPTOCHROME1/2 proteins (the negative limb members). With regard to phase entrainment, it was initially believed that only the suprachiasmatic nucleus (SCN) was capable of generating circadian rhythms. However, circadian oscillators have recently been discovered in many peripheral tissues. In the absence of a functional SCN pacemaker, these peripheral clocks dampen after a few days. Hence, the SCN must periodically synchronize these subsidiary timekeepers. It may accomplish this task mostly through an indirect route: namely, by setting the time of feeding. In addition to feeding cycles, body temperature rhythms and cyclically secreted hormones might also serve as zeitgebers for peripheral clocks.

PMID:14712916[PubMed - indexed for MEDLINE]