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REVIEW

Circadian pacemakers in mammals: a review

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Abstract: The mammalian circadian timing system is composed of almost as many individual clocks as there are cells. Several studies have been addressed, in invertebrates and lower vertebrates, to the issue of circadian rhythms in peripheral tissues. These suggest evidence that circadian rhythms are driven by cell-autonomous circadian oscillators, often light sensitive. This review has attempted to clarify the discussion of circadian systems in mammals and the issue of multiple circadian oscillators in their body thus suggesting that circadian oscillation properties are not exclusive to neural tissue or cells.

Key words: biological clock, circadian pacemaker, peripheral oscillators, mammals, rhythmically expressed genes.

Abbreviations: DD, 24 hours of dark; LD, light/dark; SCN, suprachiasmatic nucleus.

Introduction

Biological rhythms affect a variety of activities in nature, such as the sleep-wake cycle, migratory behavior in birds, seasonal fattening, hibernation and reproductive cycles in wild animals (PICCIONE & CAOLA, 2002).

Daily rhythms are controlled by self-contained circadian clocks within animal organisms. Among the components of the multifrequency rhythm spectrum, circadian rhythms have attracted greater interest because of their higher amplitude and clear relation to the light-dark cycle. The term circadian reflects the observation that under constant external conditions (without time cues) the rhythms free-run with an endogenous period close to, but not identical, to 24 h.

Here, some of the most important research developments, that have helped to improve the understanding of circadian rhythms, are reviewed.

Several approaches to elucidate the nature of biological clocks, particularly circadian rhythms, have emerged over the years. These include the attempt to locate the anatomical loci responsible for generating these periodicities, the effort to trace the entrainment pathway for light signals (and other "Zeitgebers") from the photoreceptor(s) to the clock itself.

The results obtained by these experimental lines of attack, in turn, have provided the grist for several classes of biochemical and molecular models for autonomous circadian oscillators (EDMUNDS, 1994).

Circadian pacemakers

Two defining hallmarks of circadian pacemakers are that they generate rhythms endogenously and that they are synchronized to the external environment (QUINTERO et al., 2003).

Circadian pacemakers act as individual independent clocks in each cell cooperating to generate an as yet unknown timing signal used by the body as a whole (BROWN & SCHIBLER, 1999).

For many years after the discovery of the suprachiasmatic nucleus (SCN) in 1972, the mammalian circadian system appeared to be monolithic in having only one chief central pacemaker. The central driving oscillator of the SCN was viewed as a major evolutionary change from the multiple-oscillator and multiple-photic-imput arrangements seen in all other vertebrate groups. Then intriguing new data in mammals suggested that independent local oscillatory systems existed outside the SCN (DUNLAP, 2004).

The initial findings of clock gene rhythms in peripheral tissues and fibroblasts significantly extended our view of circadian organization at the whole-organism level (BRANDSTAETTER, 2004). In mammals, the circadian clocks are present in a variety of tissues and cells, and these cell-autonomous oscillators appear to be organized in a hierarchical manner (REPPERT & WEAVER, 2002; SCHIBLER & SASSONE-CORSI, 2002).

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