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Review Paper

Melatonin: Both master clock output and internal time-giver in the circadian clocks network

Paul Pevet *, Etienne Challet

Institut des Neurosciences Cellulaires et Intégratives, Département Neurobiologie des Rythmes, UPR 3212 CNRS, Université de Strasbourg, France

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ABSTRACT

Daily rhythms in physiological and behavioral processes are controlled by a network of circadian clocks, reset by inputs and delivering circadian signals to the brain and peripheral organs. In mammals, at the top of the network is a master clock located in the suprachiasmatic nuclei (SCN) of the hypothalamus, mainly reset by ambient light. The nocturnal synthesis and release of melatonin by the pineal gland are tightly controlled by the SCN clock and inhibited by light exposure. Several roles of melatonin in the circadian system have been identified. As a major hormonal output, melatonin distributes temporal cues generated by the SCN to the multitude of tissue targets expressing melatonin receptors. In some target structures, like the *Pars tuberalis* of the adenohypophysis, these melatonin signals can drive daily rhythmicity that would otherwise be lacking. In other target structures, melatonin signals are used for the synchronization (i.e., adjustment of the timing of existing oscillations) of peripheral oscillators, such as the fetal adrenal gland. Due to the expression of melatonin receptors in the SCN, endogenous melatonin is also able to feedback onto the master clock, although its physiological significance needs further characterization. Of note, pharmacological treatment with exogenous melatonin can synchronize the SCN clock. From a clinical point of view, provided that the subject is not exposed to light at night, the daily profile of circulating melatonin provides a reliable estimate of the timing of the human SCN. During the past decade, a number of melatonin agonists have been developed for treating circadian, psychiatric and sleep disorders. These drugs may target the SCN for improving circadian timing or act indirectly at some downstream level of the circadian network to restore proper internal synchronization.

Contents

1. Introduction

In humans, disorders of rhythmicity are characteristic of, and may underlie, a variety of troubles. For example, sleep and

* Corresponding author. Address: Institut des Neurosciences Cellulaires et Intégratives, Département Neurobiologie des Rythmes, UPR 3212 CNRS, Université de Strasbourg, 5 rue Blaise Pascal, 67084 Strasbourg, France.
E-mail address: pevet@inci-cnrs.unistra.fr (P. Pevet).

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circadian rhythms are often disrupted in neurological disorders. Increasing evidence indicates that alterations in the sleep/wake cycle is associated with (or may be responsible for) many types of neurological or psychiatric disorders. Epidemiological studies demonstrate that altered re-synchronization to local time (jet-lag or shift-work rotation) has deleterious consequences and is often associated with general malaise (especially insomnia), decrements in work productivity and increases in accidents. This field of research is rapidly expanding, and disturbances of circadian functions are also known to impair processes resulting in metabolic disorders (obesity, diabetes, hypercholesteremia), as well as cardiovascular disease and cancer (Karlsson et al., 2003; Schernhammer et al., 2006; Sookoian et al., 2007; Dochi et al., 2009). The importance of circadian (also seasonal) rhythmicity for human health and welfare is becoming increasingly recognized. Developing counteractive strategies to treat, prevent or delay such disturbances is a new challenge for science and medicine. This task requires a more complete knowledge of the circadian timing system. Nowadays, it is known that a complex multi-oscillatory circadian network governs optimal and anticipatory temporal organization of functions. During the past decade, the prospects of manipulating the melatonin system to treat patients have been enhanced. In this review, we will present the circadian system and further detail the role of melatonin in regulating clock-controlled circadian rhythms.

2. The mammalian circadian system: a network of circadian clocks

Daily rhythms in physiological and behavioral processes are a common feature in living organisms. These rhythms are not just a passive consequence of cyclic fluctuations in the environment, but relies on a complex network comprising circadian clocks, synchronizing inputs, various outputs as well as multiple central and peripheral oscillators (Takahashi, 2004; Mendoza and Challet, 2009; Dibner et al., 2010). This circadian network permits optimal and anticipatory temporal organization of biological functions in relation to periodic changes of the environment.

In mammals, the focal point of this system is a master clock within the suprachiasmatic nuclei (SCN) of the hypothalamus (Fig. 1). Most SCN neurons display spontaneous circadian rhythms

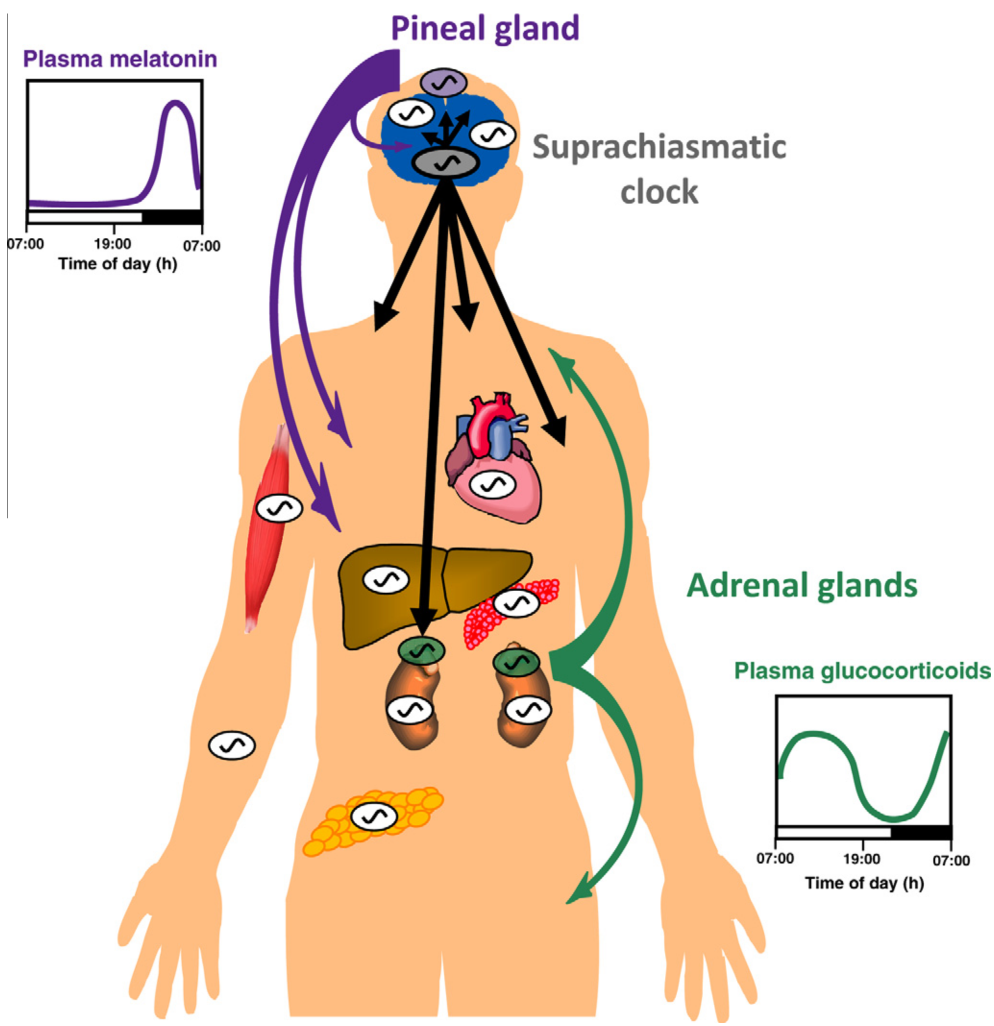

Fig. 1. The master circadian clock is located in the suprachiasmatic nuclei (SCN) of the hypothalamus. Many secondary clocks or oscillators are found in the brain and peripheral tissues. Black arrows are examples of circadian signals transmitted by nervous fibers from the SCN clock to brain and peripheral targets. Melatonin (purple) is synthesized by the pineal gland and secreted exclusively at night, under the tight control of the SCN clock. As a major hormonal output, the daily rhythm of plasma melatonin distributes temporal cues generated by the SCN to the multitude of tissue targets expressing melatonin receptors. Glucocorticoids (green) are synthesized by the adrenal glands and secreted mainly around activity onset (dawn and dusk in diurnal and nocturnal species, respectively). As another hormonal output of the SCN, the daily rhythm of plasma glucocorticoids also distributes temporal cues generated by the SCN to numerous tissue targets expressing glucocorticoid receptors.