Best Practice & Research Clinical Endocrinology & Metabolism xxx (2017) 1–13

Contents lists available at ScienceDirect

Best Practice & Research Clinical Endocrinology & Metabolism

journal homepage: www.elsevier.com/locate/beem

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The hormone melatonin: Animal studies

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ARTICLE INFO

Article history:
Available online xxx

Keywords:
melatonin
suprachiasmatic nucleus
circadian clock
circadian rhythms
chronobiotic effect

The Melatonin (MLT), secreted rhythmically by the pineal, is an efferent hormonal signal of the circadian clock. MLT presents overall pleitropic effects but it is the role of MLT as a hormonal circadian signal which is the best documented. MLT-receptors are present in numerous structures/organs and the MLT is now considered as an endogenous synchronizer within the circadian system. The presence of MLT-receptors within the circadian clock, explains that exogenous MLT is a chronobiotic drug. Trials in humans, have confirmed the efficacy of MLT in circadian rhythm disorders. Subtypes of MLT-receptors have been characterized (MT1 and MT2). Striking differences are observed in the distribution pattern of these 2 subtypes. Up to now, MTL-analogues commercialized as drugs, are all non-specific MT_1/MT_2 agonists acting on the SCN. The development of new specific agonists/antagonists for both subtypes, the identification of the link between MLT target sites within different parts of the brain or the body and the association of specific MLT receptor subtypes and particular physiological effects open great therapeutic potential.

Introduction

Experiments in animals as well as epidemiological studies in humans demonstrate that disruptions of rhythmicity cause a variety of pathologies (such as depression and cancer) and impair metabolism and cardiovascular functioning [1–3]. The mechanism used for the daily coordination of physiological

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https://doi.org/10.1016/j.beem.2017.10.010
1521-690X/

and cellular functions is far from being well understood. We know however, that in mammals a complex hierarchically organized multi-oscillatory circadian network characterized by a master clock located in the suprachiasmatic nuclei (SCN) of the hypothalamus, governs optimal and anticipatory temporal organization of functions. The SCN clock signals are forwarded via nervous and endocrine pathways to specialized structures [4]. One important structure in this network is the pineal gland, which synthesizes and secretes the hormone melatonin (MLT) at night. It is the finding that MLT was both a SCN clock output and internal time-giver in the circadian clock network [4] which strongly suggested that a major function of MLT was to act as a 'time-giver" in the multi-oscillatory circadian network. In the present review we will focus on the role and mechanisms of MLT in this specific context. (see Fig. 1)

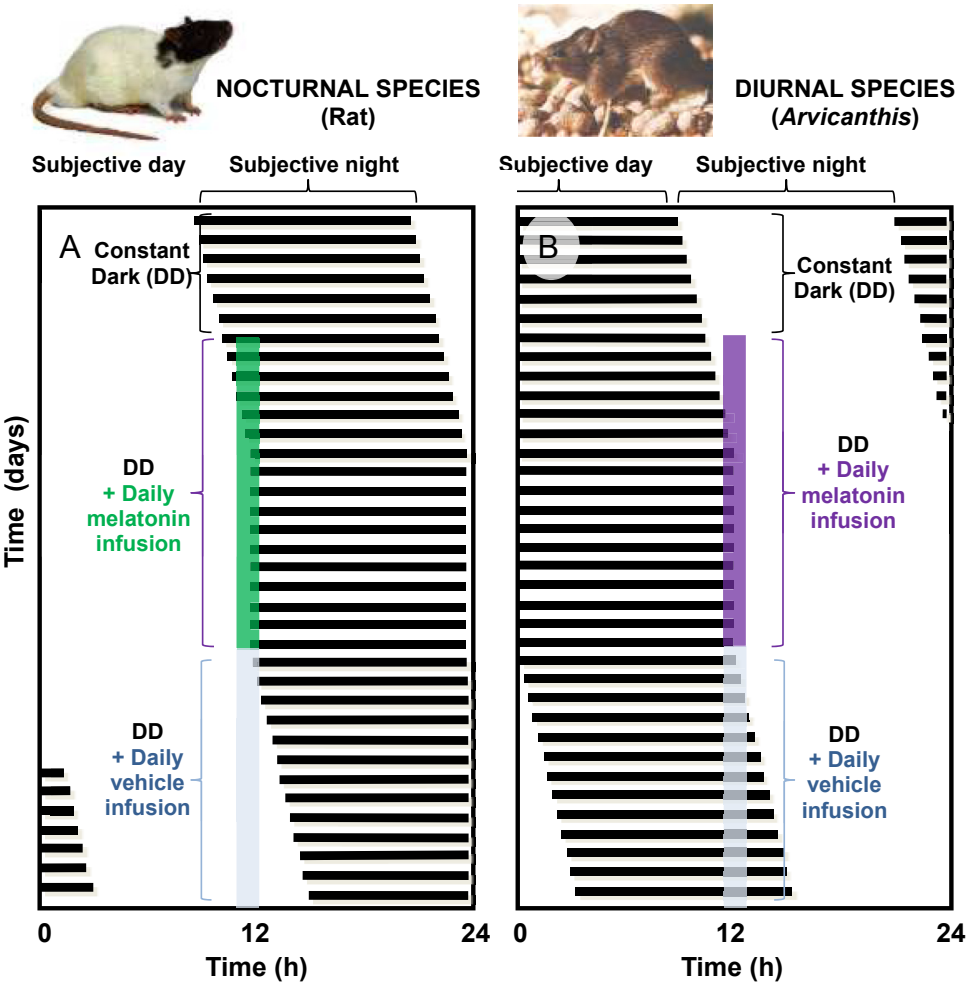

Fig. 1. In nocturnal rats free-running in constant darkness (DD) (the clock is not synchronized to 24H by the Light-dark cycle), a daily 1-h exposure to melatonin synchronizes the timing of locomotor activity by signaling "nighttime (i.e. when there is a temporal coincidence between melatonin exposure and activity onset. In Arvicanthis free-running in constant darkness, a daily 1-h exposure to melatonin also synchronizes the timing of locomotor activity by signaling "nighttime" (i.e. when there is a temporal coincidence between melatonin exposure and activity offset since Arvicanthis is a diurnal mammal. The circadian rhythm of locomotor activity is schematized by horizontal black bars to a period of 24H. The circadian locomotor activity is homologous to the sleep wake cycle in the human (Modified from Pevet and Challet, 4).

Please cite this article in press as: Pevet P, et al.The hormone melatonin: Animal studies, Best Practice & Research Clinical Endocrinology & Metabolism (2017), https://doi.org/10.1016/j.beem.2017.10.010