Melatonin and circadian control in mammals

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Summary. Although pinealectomy has little influence on the circadian locomotor rhythms of laboratory rats, administration of the pineal hormone melatonin has profound effects. Evidence for this comes from studies in which pharmacological doses of melatonin are administered under conditions of external desynchronization, internal desynchronization, steady state light-dark conditions, and phase shifts of the zeitgeber. Taken together with recent findings on melatonin receptor concentration in the rat hypothalamus, particularly at the level of the suprachiasmatic nuclei, these results suggest that melatonin is a potent synchronizer of rat circadian rhythms and has a direct action on the circadian pacemaker. It is possible, therefore, that the natural role of endogenous melatonin is to act as an internal zeitgeber for the total circadian structure of mammals at the level of cell, tissue, organ, whole organism and interaction of that organism with environmental photoperiod changes.

Key words. Melatonin; synchronization; phase adjustment; photoperiod; receptors; phylogeny; ontogeny; circadian rhythms; zeitgeber.

Introduction

As with other vertebrates, investigations into the function of the mammalian pineal body have concentrated primarily on the role played by the chemical melatonin.

Melatonin is released into the general circulation during the hours of darkness, irrespective of whether the species is nocturnal or diurnal in its behavioural activity pattern.

References

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Measurement of pineal N-acetyltransferase activity, the enzyme which drives the pineal melatonin rhythm, shows that it directly approximates circadian output from the suprachiasmatic nuclei (SCN) located in the anterior hypothalamus. The SCN are the major central nervous system (CNS) pacemakers responsible for generating circadian rhythmicity in mammals and are entrained to the external light-dark (LD) cycle by their own retinohypothalamic pathway. Therefore, while the pineal and SCN are anatomically distant and are connected by a circuitous route, the argument can be made that melatonin release is functionally part of SCN output. Because of its periodic release and its mirroring of SCN metabolic activity, melatonin is the ideal circadian chemical messenger to act as an internal zeitgeber, thereby imposing synchronicity on the multitude of daily rhythms at the level of cell, tissue and organ, and thereby preventing internal desynchrony.

Nature has selected melatonin to fulfill different synchronization roles and thereby solve different synchronization problems in different species. However, while synchronization problems in temporal organization may seem superficially different, essentially the same strategy can be used to solve them. From cell cycles to seasonal cycles a daily periodic signal is needed within the internal milieu to carefully to adjust phase between critical rhythms at all levels of temporal organization. The most researched example of this is found in photoperiodic time measurement of seasonally breeding, photosensitive mammalian species, where melatonin's action as an internal zeitgeber can be described in terms of internal or external coincidence models depending upon the species. Nature has selected melatonin to fulfill different synchronization roles and thereby solve different synchronization problems in different species. However, while synchronization problems in temporal organization may seem superficially different, essentially the same strategy can be used to solve them. From cell cycles to seasonal cycles a daily periodic signal is needed within the internal milieu to carefully adjust phase between critical rhythms at all levels of temporal organization. The most researched example of this is found in photoperiodic time measurement of seasonally breeding, photosensitive mammalian species, where melatonin's action as an internal zeitgeber can be described in terms of internal or external coincidence models depending upon the species.

Below, after a consideration of the results of pinealectomy (Px) studies, the evidence for internal zeitgeber properties of melatonin in mammals is marshalled. The bulk of this evidence comes from studies on laboratory rats and this is reviewed together with crucial findings of melatonin receptor location in the hypothalamus. Finally, alternative explanations are considered.

The pineal and synchronicity: effects of pinealectomy

Pinealectomy has little effect on rat or hamster free-running locomotor rhythms in constant light (LL) or constant dark (DD) (see Armstrong for references). It is reasonable to conclude that the pineal body is not involved in the generation of rodent circadian locomotor rhythms although this cannot be generalized to all mammals until a greater variety of species has been studied. Nevertheless, the commonly drawn conclusion that the pineal body should be relegated to a minor role in the mammalian circadian system does not necessarily follow. Removal of an organ is not always the most instructive way of assessing its biological importance.