The large daily rhythm in circulating melatonin levels is a highly conserved feature of vertebrate physiology: high values always occur at night. The dynamics of the rhythm are controlled by the next-to-last enzyme in melatonin synthesis (serotonin → N-acetylserotonin → melatonin), arylalkylamine N-acetyltransferase (AANA T), the “melatonin rhythm enzyme”. In vertebrate biology, AANA T plays a unique time-keeping role as the molecular interface between the environment and the hormonal signal of time, melatonin. This chapter describes the mammalian AANA T regulatory system, which includes the retina, neural structures, transsynaptic processes, and molecular events. In addition, special attention is paid to the functional characteristics of the systems which insure that the nocturnal increase in melatonin is an accurate and reliable indicator of the duration of the night, and why the melatonin rhythm is the most reliable output signal of the Mind’s Clock.

Keywords Pineal gland · Melatonin · Arylalkylamine N-acetyltransferase · Circadian · Second messenger · Signal transduction

Introduction

The daily rhythm in melatonin is a conserved feature of vertebrate physiology, with high values always occurring at night in the dark and never during the day. This signal plays an important role in physiology, especially in those species in which seasonal changes in reproduction are regulated by seasonal changes in environmental lighting (Karsh et al. 1991; Arendt 1995; Barrell et al. 2000). In addition, melatonin can play an entraining role in circadian physiology (Redman et al. 1983; Arendt 1995; Sack et al. 2000; Pévet et al. 2002).

The precision and reliability of the photoneuroendocrine transduction which regulates the melatonin production system, the melatonin rhythm generating system, is determined by mechanisms which operate at several levels to insure integrity of the melatonin signal. The molecular interface between regulation and melatonin synthesis is the next-to-last enzyme in melatonin synthesis, arylalkylamine N-acetyltransferase (AANA T; Fig. 1). This chapter describes the melatonin rhythm generating system in mammals, highlighting features that insure accuracy and reliability.
Accordingly, the cellular rate of $O$-methylation is largely a function of substrate availability, whereas the $N$-acetylation step is regulated by the amount of active AANAT protein. The major features of the 24-h pattern of pineal indole metabolism outlined in Fig. 1 are conserved among mammals and all other vertebrates.

Although it is clear that large changes in AANAT activity are responsible for the daily rhythm in pineal indoles, it is not clear what limits the minimum daytime and maximal nighttime rates of melatonin production. The determining factor could be the availability of cofactors, uptake of tryptophan, or the activity of other enzymes required for the conversion of tryptophan to melatonin (Klein and Weller 1970; Kapatos et al. 1981; Furukawa et al. 1993; Ribelayga et al. 2000; Martinez et al. 2001).

Rapid effects of light

A striking feature of pineal indole metabolism is the exquisite sensitivity it exhibits to light exposure at night, which causes remarkably rapid changes (Fig. 1). The critical perturbation is a rapid decrease in AANAT activity ($t_{1/2}$ ca 3 min; Klein and Weller 1972). This leads to a sharp decrease in the conversion of 5-HT to NAS and melatonin, resulting in a return to the daytime pattern of metabolites and level of circulating melatonin (Illnerová 1971; Illnerová et al. 1979; Mefford et al. 1983; Namboodiri et al. 1985).

The relationship between melatonin synthesis and circulating melatonin

Melatonin is highly lipophilic and is not stored at significant levels. Accordingly, it is released into the blood immediately upon synthesis. This close relationship between production and release is one of two factors that explain why rapid changes in melatonin synthesis are rapidly translated into similar changes in circulating levels of melatonin (Illnerová et al. 1978). The second is hepatic uptake, 6-hydroxylation, and subsequent metabolism (Kopin et al. 1961; Iguchi et al. 1982). Accordingly, circulating melatonin levels reflect a dynamic balance of production-regulated release and rapid hepatic destruction:

$$\text{Production} \rightarrow \text{Release} \rightarrow \text{Circulating melatonin} \rightarrow \text{Hepatic destruction}$$

The neural circuit regulating rhythms in pineal metabolism

All circadian systems include a circadian oscillator, a photodetector, and an output signal. In the case of the melatonin rhythm generating system, these elements and the neural connections linking them have been described in detail (for review, see Klein et al. 1991). This complete description makes the melatonin rhythm generating system unique among mammalian circadian systems.

The oscillator in the melatonin rhythm generating system is located in the suprachiasmatic nuclei (SCN; see Gillette and Mitchell 2002), the master circadian os-