Control of the daily melatonin rhythm: A model of time distribution by the biological clock mediated through the autonomic nervous system
Perreau, S.M.

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Summary

In mammals, numerous physiological, behavioural and endocrine functions show an endogenous rhythmicity close to 24-h, but precisely synchronised at 24-h by the light/dark cycle of the environment. These so-called circadian (circa = about and dies = day) rhythms are under the control of a master biological clock, located in the suprachiasmatic nucleus of the hypothalamus (SCN). The SCN (1) generates and sustains an endogenous rhythm of neuronal activity of approximately 24-h, (2) perceives and integrates photic and non-photic information for an optimal synchronisation of this endogenous rhythm with the environment, and (3) distributes this integrated temporal message to the rest of the brain and the organism.

By coordinating the activity of such a vast amount of physiological functions, the SCN is a real bodyguard of temporal homeostasis within the body. However, the fine details of the distribution mechanisms that the SCN is using for this purpose are still to be defined. Indeed, the different physiological functions show a multitude of timings for their maximal activity, whereas the main activity of the SCN neurons has so far been reported to be restricted to the light period.

In order to further understand the mechanisms of time distribution by the SCN, in the present thesis the circadian control of the extremely stable daily rhythm of melatonin release was studied as a model of clock functioning. We aimed to determine the exact effect of the SCN on melatonin synthesis, as well as the nature of the transmitters involved in this control.

Our starting hypothesis stated that “The SCN controls the daily rhythm of melatonin synthesis by imposing an inhibitory signal, of GABA-ergic nature, onto the PVN→pineal pathway during (subjective) daytime”, assuming that (without inhibition from the SCN) the PVN would provide a constant stimulatory input to the sympathetic system.

In the first study, presented in Chapter 2, we therefore compared the respective effects of lesioning or removing the SCN, the PVN or the SCG on Aa-NAT gene expression, which reflects melatonin synthesis the best. Interestingly, in contrast with our “inhibition” hypothesis, the results obtained revealed that both acrophase and nadir of the melatonin rhythm are driven by the SCN, and that PVN and SCG play a simple role of relay-station to the pineal gland. Consequently, we updated our hypothesis and proposed that: “The SCN uses a combination of both inhibitory (during daytime) and stimulatory signals towards the PVN→pineal pathway to control the daily rhythm of melatonin synthesis”, suggesting, for the first time, a functional role for the nocturnal activity of the SCN. Since its main activity period (metabolic and electric) is situated in the (subjective) light period, the SCN had until then been commonly considered a
daytime functioning structure. Hence, it appeared necessary to check the concept of a nocturnal stimulatory SCN output in an acute and in vivo situation. In addition, it was of great interest to identify the (chemical) nature of this stimulatory signal coming from the SCN. These two points were successively addressed in the second study, presented in Chapter 3, using the multiple microdialysis technique. At first, we tested the effect of an acute and temporary shutdown of either PVN or SCN electrical activity on melatonin release. Thereby, we confirmed that the nocturnal electrical firing of SCN neurons was a sine qua non condition for the nocturnal rise of pineal melatonin release. In addition, we showed an important role of glutamatergic signalling from the SCN to the PVN-pineal pathway on the melatonin rhythm generating system.

Together, the results of Chapters 2 & 3 strongly suggest that without input from the biological clock the baseline activity of the pre-autonomic neurons controlling melatonin synthesis is rather low, and that the SCN provides a continuous stimulation of the pre-autonomic neurons which are at the origin of the sympathetic activity. According to that idea, the morning decline of melatonin would be due to an increasing release of GABA onto the pre-autonomic PVN neurons. In Chapter 4, we showed that a further refinement of the GABA/glutamate hypothesis is necessary in order to explain the early morning decrease of melatonin. As it turned out, a blockade of the GABA-ergic signalling within the PVN during the dark/light transition was unable to prevent the early morning decline of melatonin completely, suggesting either a withdrawal of the glutamatergic stimulatory input at that time or the existence of a second inhibitory SCN signal involved in the control of the daily melatonin rhythm and specifically released at the dark/light transition.

During the course of the above experiments some evidence appeared in the literature for multiple clock outputs as well as for a clear compartmentalisation of the SCN. Therefore, it became of great interest to couple the activation of specific subsets of SCN cells with the onset/offset of melatonin synthesis. This aim was pursued in Chapter 5. In this chapter, we investigated whether we could correlate Per1 and Per2 gene expression in SCN neurons with the reappearance of either the onset or offset of the melatonin peak after an 8h advance of the light/dark cycle. In this chapter, we revealed different subpopulations of SCN neurons that may be dedicated to the control of the daily melatonin rhythm. In addition, the results of this chapter suggest that expression of the Per2 gene in the SCN might be more closely linked to SCN output (i.e. locomotor behaviour and VP release) than that of the Per1 gene.

Altogether, the studies presented in this thesis reveal an updated concept of the control of the daily melatonin rhythm by the biological clock. More importantly, the new concept for the SCN control of the melatonin rhythm may help to understand how the SCN controls the autonomic nervous system. This is all the more interesting since recent tracing studies provided evidence for neuronal connections between
the SCN and various peripheral organs (i.e. liver, pancreas, thyroid, spleen, and fat tissue), suggesting that the autonomic nervous system may be an important system for the SCN to distribute its time-of-day message to many other physiological and hormonal rhythms.