Cardiovascular control by the biological clock
Scheer, F.A.J.L.

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SUMMARY

A proper functioning of the cardiovascular system is essential for life. Blood circulation provides all tissue with nutrients and oxygen and allows disposal of toxic waste products. Along with the day-night rhythm in behavioral and physiological activity, the circulatory requirements, too, fluctuate with day and night.

The main research question in the present thesis is if and how the biological clock (located in the suprachiasmatic nucleus, SCN) influences the cardiovascular system. The influence of the biological clock was investigated in two ways: Firstly, the endogenous circadian (circa: about, dies: day) rhythm of the cardiovascular system was investigated because the SCN is responsible for endogenous circadian rhythms. Recording under conditions that excluded the effect of "masking" factors of the cardiovascular and circadian system, such as behavioral activity and light, made this type of research possible. Secondly, the effect of changing the activity of the biological clock on the cardiovascular system was investigated. Two stimuli to affect the SCN were used: light as the day-signal and melatonin as the night-signal for the biological clock. The results of the present studies revealed that the biological clock influences the cardiovascular system via both neuronal and endocrine mechanisms.

We showed that there is an endogenous circadian rhythm in HR in human and rat, thus without the disturbing influences of behavioral activity and light exposure (Chapters 2 and 4). As expected for a SCN-induced rhythm, the rhythm in resting HR in (day-active) human showed a peak during the day and a trough at night, while the rhythm in (night-active) rat was the exact opposite of this. The critical role of the SCN in this rhythm was demonstrated in animal experiments, by the disappearance of the circadian rhythm in HR after lesioning of the SCN (Chapter 2). Next, we demonstrated that light - as day-signal to the SCN - during the night resulted in day-time HR levels, and thus in an increase in HR in human and a decrease in rat (Chapters 2 and 4). That the change in HR caused by light depends on the species being day- or night-active assures us that the effect is not an a-specific startle effect. In humans, both a dose-dependent and phase-dependent stimulation by light was demonstrated, which further suggests the involvement of the SCN (Chapters 4). The critical role of the SCN could be proven in animal experiments by lesioning of this nucleus, which completely blocked this effect of light on HR (Chapter 2). Apart from this physiological evidence for the effect of the SCN on the heart, the neuronal connection from the SCN to the heart was demonstrated with the use of transneuronal virus tracing (Chapter 2). This multisynaptic projection via the autonomic nervous system provides an anatomical substrate via which the SCN could impose the circadian rhythm and the effect of light on the heart. To investigate the role
of sympathetic and parasympathetic cardiac outflow in the circadian rhythm in heart rate, and the effect of light on heart rate, we recorded non-invasive indices for both branches of the autonomic nervous system in humans under repeated routine conditions (Chapter 5). We showed that in humans, the circadian rhythm in resting HR was due to the circadian rhythm in parasympathetic cardiac activity and that the sympathetic nervous system caused the increase in heart rate as a result of early morning light.

Body temperature changes are the product of changes in heat production and heat loss. Heat loss is controlled for an important part via vasodilatation and vasoconstriction of the skin, that affects the exchange of heat from the warm blood to the (normally) cooler environment. In this way, the vascular system is involved in both blood pressure and temperature regulation. In Chapter 3, we demonstrated the presence of an endogenous circadian rhythm in temperature that was independent of locomotor activity. The circadian rhythm in body temperature disappeared in SCN-lesioned rats, demonstrating the crucial role of the SCN. Furthermore, a circadian phase-dependent inhibitory effect of light on temperature was demonstrated, suggesting a role of the SCN. Indeed, lesioning the SCN abolished this phase dependent effect of light. Although lesioning of the SCN abolished the effect of light on temperature, the effect slowly reappeared over 6 months in LD, but without any recovery of an endogenous rhythm (in DD). This recovery of effect of light on body temperature with only a weak effect on other SCN-driven rhythms (i.e. HR and LA) indicates that certain brain areas (e.g. the MPO and/or Edinger-Westphal nucleus) can take over the function of the SCN to pass on the effect of light on BT, but not on other SCN-driven rhythms. The gradual reappearance (over months) of the effect of light, that can mimic the day-signal of the SCN under LD conditions, may explain the controversy in the literature concerning the question whether the daily rhythm in temperature is generated by the SCN.

Apart from this regulation by the autonomic nervous system, the cardiovascular system is influenced also by hormones. We investigated the role of hormones as signal from the biological clock. Glucocorticoids (mainly cortisol in human, and corticosterone in rat) are hormones that prepare the body for impending activity, not only after stress, but also in anticipation of the daily activity period. Glucocorticoids have a clear circadian rhythm, which has been demonstrated in rodents to be dependent on the presence of the SCN. The morning cortisol surge in humans increases blood glucose and causes a rise in BP. In rats, light affects corticosterone secretion depending on the phase of the day and depending on the SCN. To test the involvement of the SCN in humans we investigated whether light also affects cortisol levels in a phase-dependent manner in humans, which would suggest a role of the SCN in cortisol secretion also in humans (Chapter 6). Moderate light intensity (800 lux) enhanced the cortisol peak in the early morning by 35%, while light in the evening had no effect. The phase-dependency of the effect supports the hypothesis that also in humans the effect of light on cortisol is mediated via the
SCN. In our everyday life, the endogenous morning signal of the SCN may be further enhanced by light in the morning, resulting in a further improved preparation of the cardiovascular system and other organ systems for the activity period.

The hormone with the strongest day-night amplitude is melatonin. It shows an endogenous circadian rhythm with a peak at night and very low levels during the day. Melatonin is produced and secreted by the pineal gland, which is under the exclusive control of the SCN. Melatonin acts as the nighttime signal from the SCN to the rest of the body, including the SCN itself, closing the feedback loop. Firstly, melatonin causes an immediate inhibition of SCN neuronal activity towards nighttime levels. Secondly, daily melatonin intake in the evening can synchronize SCN neuronal activity and can restore disturbed circadian rhythmicity, also in humans. Recently, it was demonstrated in post mortem material of patients with essential hypertension that the SCN is disturbed, with a lower neurotransmitter-content than in comparison with normotensive controls. We therefore investigated if the restorative effect of a single or repeated (3 weeks daily) nighttime melatonin intake could lower BP in patients with essential hypertension (Chapter 8). Repeated bedtime melatonin intake (2.5 mg) significantly lowered systolic and diastolic BP by during sleep, respectively, 6 and 4 mm Hg. Single melatonin intake was unable to affect BP. Similarly, repeated, but not single, melatonin intake improved sleep quality and increased the amplitude of the day-night rhythm in BP. The repeated nighttime melatonin intake most likely amplified the rhythm of the SCN, which restored proper SCN-output in the regulation of the cardiovascular system, resulting in reduced BP. Alternatively or additionally, repeated melatonin intake substitutes the night-time output of the SCN to the body, possibly improving the functioning of the cardiovascular system by entraining the peripheral oscillators therein. Furthermore, these results could be seen as proof of principle for the potential benefit of melatonin in pathologies with disturbed circadian rhythmicity.

All previously mentioned human experiments (Chapters 4-6 and 8) were performed in a home setting and not in a laboratory setting. Measurements performed in the laboratory or hospital have the advantage that the investigator has maximum control over the experiment. However, the effect of the experimental setting on the outcome of the experiment is mostly unknown. The impact of a hospital setting on the cortisol rhythm is demonstrated in Chapter 7. In comparison with young healthy males studied in a home setting, young healthy males in a hospital setting demonstrated an increase in free cortisol by 3-fold during the morning peak and by at least 5-fold in the evening (all measurements during supine resting conditions in the dark). Furthermore, light was unable to further increase the already high cortisol levels in the hospital setting in the early morning, thus preventing further exploration of the neuroendocrine mechanism involved in the light-induced increase in cortisol as demonstrated in the home setting. The cortisol levels as measured in our hospital experiment were comparable with other
carefully conducted hospital experiments. These results indicate that precaution should be taken with interpreting results in a hospital setting, especially when small changes in the HPA-axis are the subject of study.

In conclusion, the present thesis demonstrates the importance of the biological clock in cardiovascular regulation via both neuronal and endocrine mechanisms, and demonstrates that light and melatonin can influence cardiovascular functioning. This provides new perspectives for the treatment of hypertension, which is characterized by circadian disturbances, by modifying the circadian system. A first application of this concept is already presented in this thesis with the blood pressure reduction through repeated nighttime melatonin intake in patients with essential hypertension.