Neuroendocrinology Letters No.6 December Vol.24, 2003

REVIEW ARTICLE

Biorhythms and pineal gland

Valér Csernus & Béla Mess

Department of Human Anatomy, Faculty of Medicine, Univ. Sci.,
and Neurohumoral Regulations Research Group of the Hungarian Academy of Sciences,
Pécs, HUNGARY.

Correspondence to: Prof. Valér Csernus,.
Department of Anatomy
University of Pécs, Medical School
Szigeti Str. 12, 7624 Pécs
HUNGARY
TEL: +36 72 536 392 FAX: +36-72 536 393
EMAIL: valer.csernus@aok.pte.hu

Submitted: *April 30, 2003*
Accepted: *November 13, 2003*

Key words: **biorhythm; endocrine rhythms; pineal gland; melatonin; mammals; birds; circadian melatonin rhythm; light impulses**

Neuroendocrinol Lett 2003; **24**(6):404–411 NEL240603R01 Copyright © Neuroendocrinology Letters **www.nel.edu**

Abstract

Endocrine biorhythms are classified according to the period time, as one of the most characteristic properties of biorhythms. Each endocrine organ has parallel more than one biorhythms with different period time (e. g. circadian and circannual rhythms). The time of acrophase of the biorhythms at the different endocrine organs is fairly variant. This review summarizes the rhythmic function of the THS-thyroid, gonadotrophic-gonadal and ACTH-adrenocortical systems.
Pineal gland plays an integrative role in the regulation of rhythmic function of the endocrine system. The melatonin secretion of this gland also reveals conspicuous circadian and circannual rhythms both in mammals and in birds. Mammalian pineal is functional only if its peripheral sympathetic innervation from the superior cervical ganglion is intact. In contrast, melatonin secretion and its circadian rhythm is also maintained in birds under isolated conditions (explanted into an in vitro superfusion system). The 24 hours period time of melatonin circadian rhythm can not be changed by light impulses. The phases of the circadian rhythm, however, can be turned by changing the time of environmental light-dark phases. The wavelength of the artificial light used for reversal of circadian rhythm is an important factor. The development of the entrainment and synchronization of the circadian melatonin rhythm in birds is independent of the rhythmic day-night changes in environmental lighting condition.
The differences in the main elements of the biological clock between mammals and birds are discussed.

Already in 1966, the Nobel prize winner Axelrod apostrophized the pineal gland in the title of one of his papers, as a “biological clock” [1]. On the other hand, in the last 30–35 years, it was recognized that the majority, nearly all of the physiological processes have rhythmic character, like heart beat, breathing, food intake, sleep-wakefulness etc. Nearly 30 years ago, a volume edited by Kawakami [2] and written by 23 contributors (including one of the authors of this review) devoted to the research of biological rhythms was bearing the title: “ Biological Rhythms in Neuroendocrine Activity”. In many of these rhythmic functions, pineal gland plays the role of a pacemaker, biological clock or regulator. Therefore, it seemed to be interesting to study the rhythmic hormone secretion of the pineal gland itself, and the biological clock character of this organ regulating the rhythms of other organ systems or functions (reproduction, orientation of migrating birds etc.). Being authors interested in comparative endocrinology, this aspect, especially similarities and differences between mammals and birds, will also be involved in this short survey. This problem was recently summarized in more details in a short monograph of the authors [3]

Among many other properties, the most characteristic parameter of the different biorhythms is the period time. It varies between seconds or milliseconds till a year or even ten years ("circadecennial rhythms") [4]. The most thoroughly investigated rhythms are the circadian and circannual biorhythms. Therefore, the experimental work of the authors, consequently the main task of this mini-review, deals primarily with these two types of rhythms.

It would be impossible to deal with all types of rhythmic physiological functions within the frame of such a short survey. Therefore, we have to restrict the scope of this mini-review to the endocrine biorhythms, or to rhythms closely related to endocrine functions.

Endocrine biorhythms

All endocrine organs have parallel at least circadian and circannual rhythms of their hormone secretion. Table I. schematically comprises the best known endocrine rhythms pointing out the time of acrophase of the given rhythm. Anterior pituitary is not listed in this table, since the rhythmic secretion of the different trophic hormones is mentioned at the corresponding different peripheral endocrine systems.

Probably the circadian rhythm of adrenocortical hormone (ACTH) secretion was the most widely studied among all endocrine biorhythms. Daily rhythm of different parameters of adrenocortical function was studied in a wide variety of species such as birds [5,6], mammals [7,8] and man [9, 10].

Besides many other parameters, blood corticosteroid determination seems to be the most reliable, and is the most frequently investigated parameter of the circadian rhythm of the ACTH-adrenocortical system. Corticosterone [8,11] cortisol [12,13] and deoxycorticosterone secretion [14] or corticosterone binding activity [15] equally show well defined circadian rhythm. Authors generally agree that the acrophase of the circadian rhythm of adrenocortical hormone secretion is at the beginning or first half of the dark phase. On the ground of concordant data of the literature, it is now a general rule, equally in clinical diagnostics and in animal experiments, that blood samples for adrenocortical hormone determinations should be taken exactly at the same time of the day. The acrophase of the circannual adrenocortical rhythm is in the short day phase of the year (Nov.– Jan.) [16].

Less conspicuous but still characteristic is the circadian and circannual rhythm of the TSH-thyroid system. The circadian rhythm of this system was equally investigated in mammals [17,18] and in birds [19, 20]. Many parameters, like TSH and T4 blood levels, thyroidal iodide uptake, mitotic rate of the thyroidal epithelial cells, were equally determined by these authors. The acrophase of the circadian rhythm of thyroid-hormone blood levels is in the light phase of the day [17, 21].

However, there are some differences, especially in the time of acrophase, in the circadian rhythms between the diurnal and nocturnal active species (human: [22, 23], rat: [17, 21]). Circannual thyroid rhythm has its acrophase in the winter months (Nov.-Dec.) in the albino rat [24].

Somewhat more complicated is the rhythm of the gonadotrophic-gonadal system. Many mammalian species and the majority of birds, reptiles and amphibia belong to the so-called seasonally breeding species. At these animals, the circannual rhythm of the gonadotrophic-gonadal system is the most conspicuous (See for references, mammals: [25], birds: [26]). Female receptivity (ovulation) and male sexual activity (spermatogenesis, sexual behavior) equally have a longer phase of sexual quiescence and a seasonally returning sexually active phase.

The time of acrophase (sexually active period) varies between ample limits, according to the length of pregnancy and the habitat (e.g. northern or southern hemisphere) at the different species. There is no space here to enter into the discussion of rhythm regulation of reproduction in the arctic [27, 28] and tropical [26] bird species. This interesting question has been recently surveyed by the authors in a Chapter of a short monograph [3].

To the so-called cyclic breeders belong quite different mammalian species (laboratory white rat, horse, human being). The length of the cycle shows wide varieties between the species (rat: 4 days, horse; 20–25 days, man 28 days). Since the exact time of ovulation is individual within the given population of the cyclic breeder species, therefore, males are steadily in sexual activity to be able to fertilize females becoming receptive in any day of the year.

The circadian rhythm of gonadotrophic-gonadal system is less conspicuous, still existing at these species; e.g. LH-release, consequently ovulation is at the early afternoon hours at the albino rat, sexual behavior at the diurnal or nocturnal species etc.

There are many data, available in the literature, indicating that pineal gland plays a crucial role in the timing and maintenance of the circadian as well as of the circannual endocrine biorhythms. Pinealectomy or melatonin treatment significantly alter both the circadian and the circannual iodo-hormone concentration of the thyroid gland. [24]. Pineal gland significantly influences also the occurrence and timing of the sexually active period in the seasonally breeding mammals (Syrian hamster: [299] birds: [30]). Sexual rhythm is considerably changing also in the cyclic breeder albino rat following manipulations on the pineal gland (See for references: [31, 32]).

Rhythmic pineal melatonin secretion, being in the focus of this short survey, will be discussed in the next chapter.

Orientation of the migratory birds is very probably strictly related with the circannual rhythm of the endocrine system. Therefore, it seems to be interesting to mention briefly also this aspect as a special example of circannual biorhythms.

The original assumption that young birds learn the route of migration from the parents was later formulated that it is a genetically coded property of the different avian species. In the last few decades, evidences were brought that earth magnetic fields serve for the orientation of migratory birds.[33]. It was shown that pineal gland is involved in the elicitation of migratory behavior ("Zugunruhe") and orientation capacity of the pied flycatcher [34]. Although, this question is far from satisfactorily be solved, it can be taken as a verified fact that pineal gland is a crucial factor in the elicitation of migratory behavior, probably by other circannual rhythmic endocrine mechanisms. Earth magnetic fields might serve as "road sign" for orientation.

Nature, mechanism and neural control of the circadian pineal melatonin secretion in mammals and birds.

There is a principal difference in the nature and regulation of pineal melatonin secretion between mammals and birds. Consequently, the regulatory mechanisms of the circadian rhythm of pineal melatonin production is also different between the two classes of animals.

Mammalian pineal is functional only if its peripheral sympathetic innervation from the superior cervical ganglion is intact, and its neuronal contact with the lateral eyes has been preserved [1, 35, 36].

Therefore, rat pineal explanted into a superfusion chamber, is capable only for a basal secretion rate of melatonin. This low basal secretion is independent of the environmental light-dark changes [37, 38]. However, these denervated mammalian pineals react with a high melatonin peak to norepinephrine (a sympathetic neurotransmitter) or to Vasoactive Intestinal Polypeptide (VIP) administration, also independently of the light-dark phases [32, 39]. Figure 1.

In contrast, chicken pineal has kept its full melatonin secreting capacity and circadian rhythm explanted into a superfusion system [40], Figure 2. The 24 hours period time of melatonin circadian rhythm can not be changed by light impulses. Shorter, 6–6 hours light-dark rhythms, or continuous darkness were ineffective. However, continuous illumination resulted in an attenuated amplitude of the daily rhythm tending to be stabilized in a steadily higher level of melatonin secretion. Figure 3.

In contrast to the very stabile period time, the phases of the circadian rhythm of pineal melatonin production can be turned by changing the time of environmental light: dark phases. Keeping explanted chicken pineals in a reversed environmental lighting schedule, the daily melatonin rhythm was also reversed with acrophase in the actual dark phase Figure 4 [41].

The wavelength of the artificial light, used for reversal of circadian rhythm of pineal melatonin secretion is also an important factor. As shorter the wavelength is, as quicker the reversal of the phases of the melatonin rhythm can be obtained. The most effective was blue, less effective green, and red light was ineffective in this respect [42] Figure 5.

The light reactivity of the avian pineal explanted into a superfusion system was thoroughly investigated, and principally similar results were obtained by Takahashi et al, [43].

The development of the entrainment and synchronization of the circadian melatonin rhythm in birds is independent of the rhythmic day-night changes in environmental lighting conditions. Chickens hatched under continuous illumination from the very first day of incubation, and newly hatched chickens were kept also in continuous light, the circadian rhythm of pineal melatonin secretion was completely normal. The light reactivity of the explanted pineals of the "illuminated" chickens (continuous light exposure, reversed light schedule etc.) was the same as that of the normal chickens [41].

Experimental input other than light, such as ambient temperature, moisture, food availability etc. might also influence circadian rhythm of pineal activity equally in reptiles [44, 45], birds [46, 47] and mammals [48]. Earth magnetic field is important in inducing seasonal migratory behavior in migrating birds [34, 49]. On the other hand, Wiltschko and Wiltschko [50] reported that pineal gland plays also an integrative role in inducing migratory behavior. In our superfusion experiments, however, artificial changes in the environmental magnetic fields failed to influence circadian melatonin secretion on chickens (Csernus and Faluhelyi, unpublished data).

On the ground of all these investigations, the following conclusions can be drown concerning the differences of the machinery of the biological clock, regulating rhythmic melatonin secretion in mammals and in birds.

The main elements of the biological clock in mammals are:

1. The input channel of the biological clock is formed by the retina of the lateral eyes and by the visual pathways [36, 51–53].
2. The pacemaker of this clock system is the suprachiasmatic nucleus of the hypothalamus. See for references: [54].
3. The output channel of this clock system is the sympathetic neural chain and the melatonin producing cells of the pineal gland.

In contrast, the same three elements of the rhythmic melatonin secretion, regulating biological clock in birds, is quite different. All three elements are located within the pineal gland. Figure 6.

Avian pineal gland has kept its direct light sensitivity (See for references [55]).

Cells similar in structure to the rod-and cone-cells of the retina were found in reptilian and avian pineal gland [56, 57]. A specific opsin (pinopsin), similar to the visual opsins of the retina, were also described in the chicken pineal [58]. So, the input channel for the light impulses in this biological clock system is the pineal gland itself.

The pacemaker. i.e. the central element of this clock is also within the pineal gland. Clock genes, present in the chicken pineal gland [59, 60] might be responsible for this function. Robertson and Takahashi [61] analyzed the nature of the circadian clock in cell culture of chicken pineal cells. A complicated intra- and intercellular mechanism was suggested by Mess and Csernus, [62] and Csernus and Mess [3] explaining the pacemaker mechanism of the avian pineal gland.

Signal transduction pathways between the clock and the melatonin synthesizing enzymes were recently studied by Csernus and Mess [3]. Chicken pineals were exposed to various drugs (forskolin, fluphenazine, suramin, thapsigargin, nipridin, etc.) which activate or inhibit known elements of the intracellular signal transduction. It was concluded that cAMP-protein kinase-A, calmodulin, nitric oxide synthase and arachidonic acid-prostaglandin system participate in the control of melatonin release from the avian pineal. These signal transduction mechanisms and the well-known process of melatonin synthesis [35] form the output channel of circadian melatonin rhythm.

There are also other considerable differences between the function and rhythm of the mammalian and of the avian pineal gland. Only the two most characteristic differences will be mentioned here.

A single short (few minutes) light impulse in the middle of the dark phase causes rapid and significant fall in the night peak of melatonin release in the living rat [63] and in the hamster [64]. Similar results were obtained in the living pigeon [65]. In contrast, the same light impulse failed to influence the diurnal rhythm of melatonin output of the superfused chicken pineal [52, 66] The explanation of this difference needs further experimental elucidation. It can be supposed that retinal light reception, responsible for the main input channel of melatonin rhythm at mammals is more sensitive and have more quick

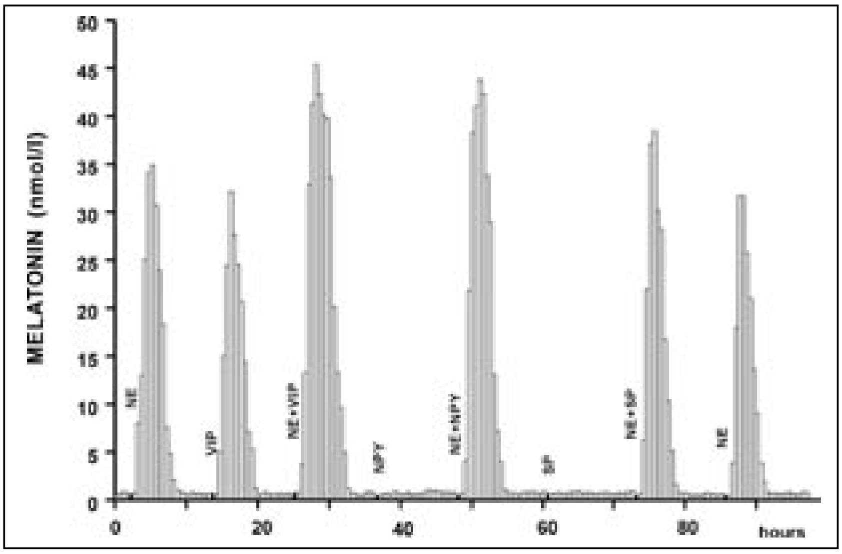

Figure 1. Melatonin secretion of the perifused rat pineal tissue following exposure to various neuropeptides for 30 minutes.

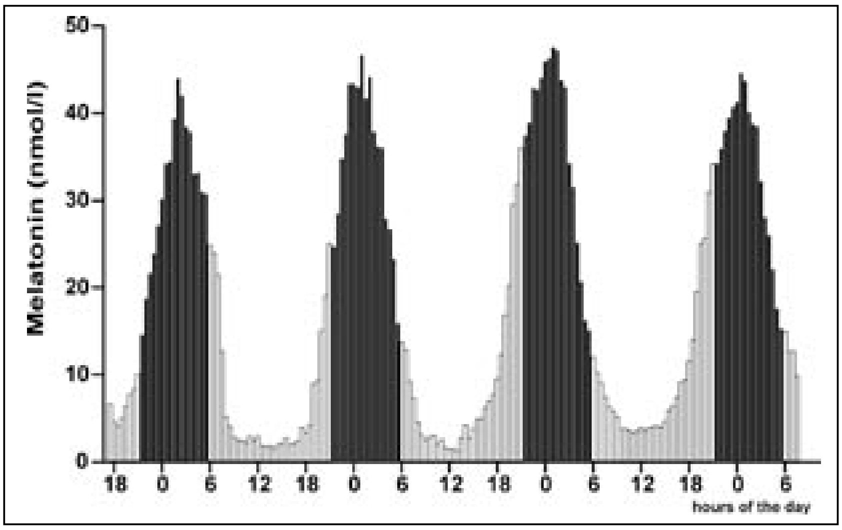

Figure 2. MT release from explanted chicken pineal tissue fragments *in vitro*. MT content of consecutive 30 minute fractions from a 5 day experiment are shown. On the horizontal axis the real time (0 = midnight) is indicated. The perifusion columns were exposed to normal light-dark environmental illumination cycle (L:D 14:10). Dark columns represent dark environment. Circadian rhythmic MT release is seen. The peaks are around midnight.

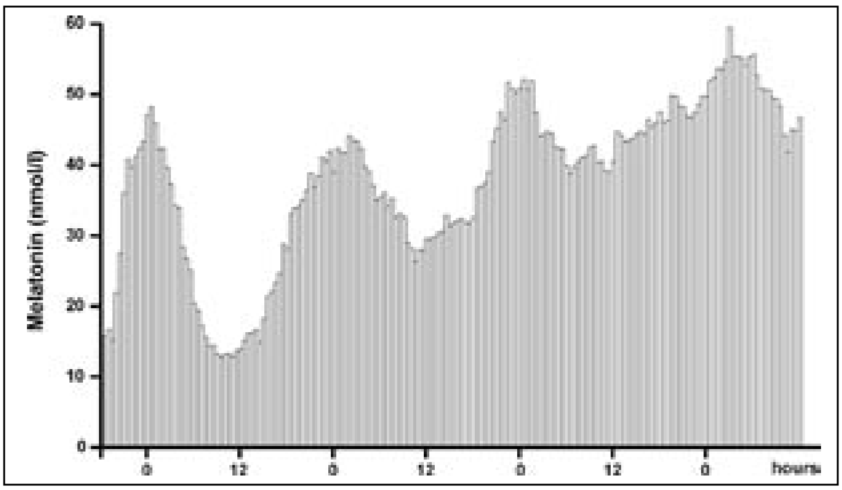

Figure 3. MT release from explanted chicken pineals. The experimental setup and the structure of the figure is similar to that of Fig. 2. This experiment was performed under continuos illumination. The amplitude of the circadian MT cycle reduces rapidly and then MT release tends to stabilize at a high level.

reactivity than the light receptor cells of the avian pineal.

The other conspicuous difference between the reactivity of the mammalian and avian pineal gland is in the response to external chemical inputs. It is generally known and accepted since decades that norepinephrine, the neurotransmitter of the postganglionic sympathetic terminals, is the most potent stimulator of pineal melatonin production in mammals [1, 35]. In contrast, this neurotransmitter is slightly inhibitory in birds under *in vitro* circumstances. [52, 66, 67]. However, an other neurotransmitter (neuro pep tide), VIP, is stimulatory in both birds [52, 68] and mammals [38, 39, 69].

Circannual rhythm of pineal melatonin secretion was also reported [24]. The highest pineal weight was measured in rats, kept under natural environmental lighting conditions, in the long-day period of the summer months, June and July. This is the period, when a low pineal activity (long-day) was expected. It was shown, however, that high pineal weight is coupled with low pineal activity (See for references [70]). The acrophase of the circannual rhythm of pineal weight and activity widely varies with species, especially at the seasonally breeder animals. This aspect was briefly summarized in the previous chapter of this survey.

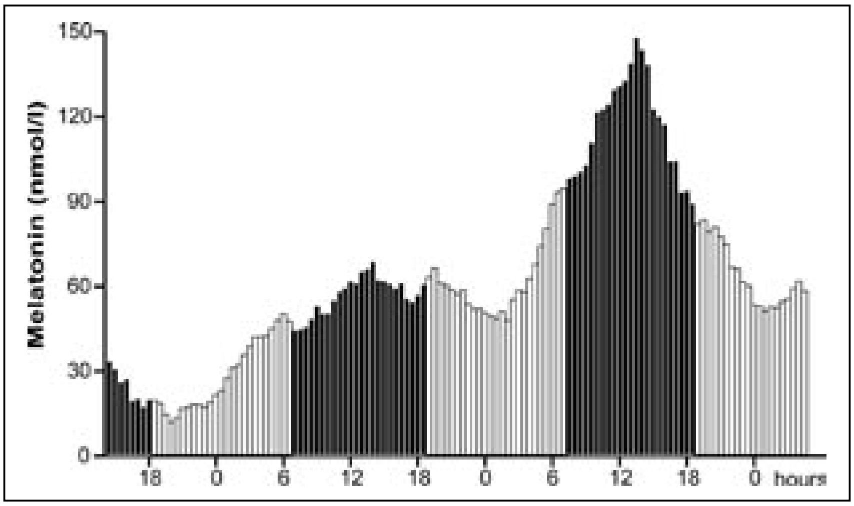

Figure 4. The effects of reversed illumination on the MT release from explanted chicken pineals. The experimental setup and the structure of the figure is similar to that of Fig. 2. The tissue was exposed to LD 14:10 illumination cycle, but in reversed phase compared to the normal light schedule. The phase of the MT release was completely reversed (180 shift) in two days.

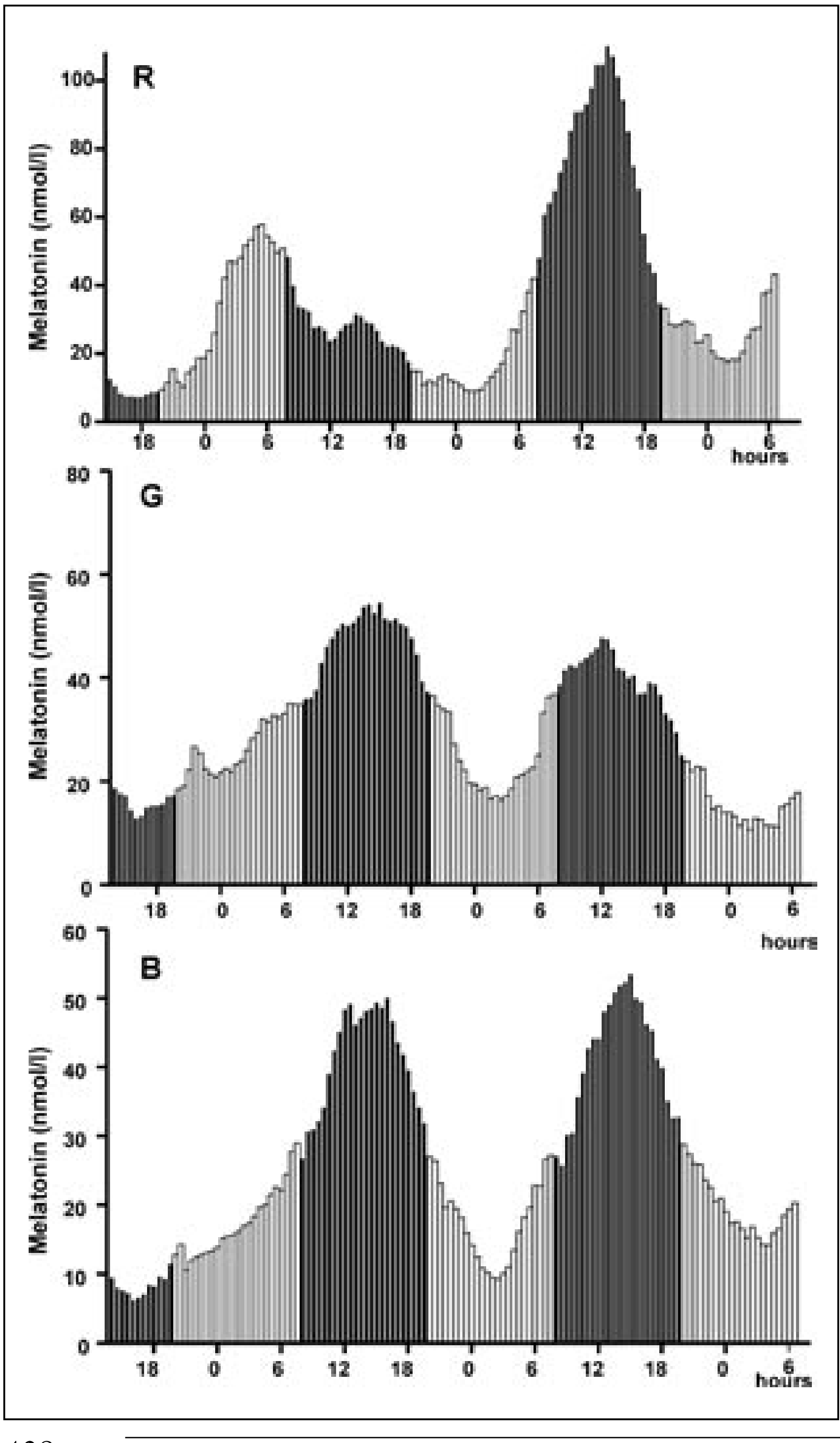

Figure 5. Spectral response of the chicken pineal gland. MT release from explanted chicken pineals are shown. The experimental setup and the structure of the figure is similar to that of Fig. 2. The perifusion columns were covered by red (R), green (G) or blue (B) filters. The intensity of the illumination was compensated by the light absorption of the filters – on the surface of the perifusion columns was 200 lux in each case. Reversed illumination was applied. Although finally the MT release was reversed in each case, but the speed of the reversal was significantly faster in case of the blue light reveling that the chicken pineal gland is most sensitive to blue light.

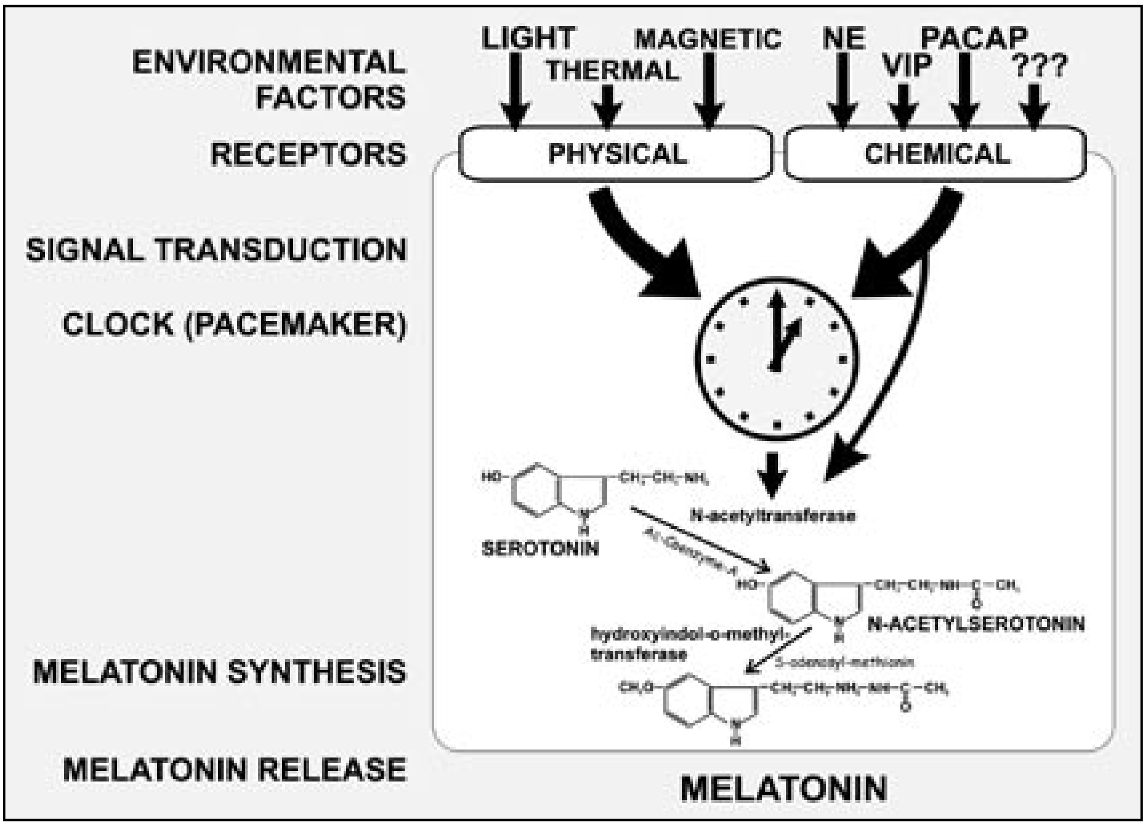

Figure 6. Schematic representation of the features of the biological clock in the avian pineal gland.

Conclusions and Summary

1 The vast majority of physiological functions show some kind of rhythm with widely different period times.

2 Endocrine organs, including pineal gland, have at least two types of rhythm: circadian and circannual rhythms.

3 The rhythmic function (melatonin secretion) of the pineal gland plays integrative role in the rhythm-regulation of other organs or organ systems, with special reference to reproduction.

4 The " biological clock ", represented by the pineal gland, consists of three main elements: input channel, central clock, output channel.

5 The mechanism and regulation of the circadian rhythm of pineal melatonin secretion is principally different in mammals and birds.

6 The three elements of the biological clock are located in mammals in three different organ systems. (1) the input channel: the retina and the visual pathways, (2) the central clock (pacemaker): the suprachiasmatic nucleus of the hypothalamus, and (3) the output channel: the sympathetic nervous system and the pineal gland.

7 The same three main elements of this clock are located in birds in a single organ, in the pineal gland. Light receptors are the rod-and cone-like pineal cells (input channel) which are coupled by a complicated biochemical machinery (pacemaker) to the melatonin producing pinealocytes (output channel).

8 Therefore, denervated (explanted) mammalian pineal is capable only for a low basal secretion rate of melatonin, but has lost its reactivity (rhythm). In contrast, avian pineal, explanted into an in vitro superfusion system, has kept its circadian rhythm and its responsiveness to changes in environmental lighting conditions.

9 The 24 hours period time of the circadian melatonin rhythm of the chicken pineal gland can not be altered principally by changes in environmental lighting conditions. However, the phase of circadian rhythm can be reversed by reversal of the daily light: dark cycle.

10 This autonomy of the rhythms and melatonin producing capacity of the avian pineal gland is not entrained by rhythmic day-night changes of environmental lighting conditions, but this is due to a genetically coded mechanism.

11 Chickens hatched and kept in continuous light throughout their lifetime, the circadian rhythm of pineal melatonin production still develops and is normally maintained.

12 Experiments, performed on in vitro superfused chicken pineals, indicate that avian pineal is an appropriate model for further studying the nature and character of different rhythmic biological functions.

REFERENCES

1 Axelrod J, Wurtman RJ, Snyder SH. Contol of hydroxy-indole-O-methyltransferase activity in the rat pineal by environmental lighting. J Biol Chem 1965; **240**:949–954.

2 Kawakami M. ed. Biological rhythms in neuroendocrine activity. Igaku Shoin Ltd, Tokyo 1974.

3 Csernus V, Mess B. The avian pineal gland. A model of the biological clock. Akadémiai Kiadó / Academic Press /, Budapest 2003; /In press/

4 Watanabe Y, Cornélissen G, Halberg F. Circadecennial human circulating variability and coherence with helio- and geomagnetic activity. Proc. 1st Internat. Symp. on Chronobiology and Chronotherapy. Kidan Chiyadoku, Tokyo. 2000. p. 101–104.

5 Ramade F, Bayle JD. Adrenocortical adaptation to chronic intermittent stress in haemispherectomized pigeon. Physiol Behav 1984; **33**:73–80.

6 Westerhof I, Van den Brom WE, Mol JA. Responsiveness of the glucocorticoid-suppressed pituitary-adrenocortical system of pigeons / Columba livia domestica/ to stimulation with arginine vasopressin. Avian Dis 1996; **40**:312–320.

7 Miyamoto H, Mitani F, Mukai K, Suematsu M, Ishimura Y. Daily regulation of rat adrenocortical cells: circadian and zonal variations in cytogenesis. Endocr Res 2000; **26**:899–904.

8 Atkinson H. C, Waddel BJ. Circadian variation in basal plasma corticosterone and adrenocorticotropin in the rat: sexual dimorphism and changes across the estrous cycle. Endocrinology 1997; **138**:3842–3848.

9 Charmandari E, Pincus S. M, Matthews DR, Johnston A, Brook CG, Hindmarsk PC. Oral hydroxycortisone administration in children with classic 21-hydroxylase deficiency leads to more synchronous joint GH and cortisol secretion. J Clin Endocrinol Metab 2002; **87**:2238–2244.

10 Kiess W, Meidert A, Dressendörfer R. A, Schriever K, Kessler U, Konig A, et.al. Salivary cortisol levels throughout childhood and adolescence, relation with age, pubertal stage and weight. Pediatr Res 1995; **37**:502–506.

11 Moberg GP, Bellinger LL, Mendel VE. Effect of meal feeding on daily rhythms of plasma corticosterone and Growth Hormone in the rat. Neuroendocrinology 1975; **19**:160–179.

12 Albers HE, Yogev L, Todd RB, Goldman BD. Adrenal corticoids in hamsters: role of circadian timing. Am J Physiol 1985; **248:**R-434–438.

13 Przekop F, Stupnicka E, Wolinska-Witort E, Mateusiek K, Ladowski B, Domanski E. Changes in circadian rhythm and suppression of the plasma cortisol level after prolonged stress in the sheep. Acta Endocrinol. /Kbh/, 1985; **110**:540–545.

14 Toitou Y, Sulon J, Bogdan A, Toitou C, Reinberg A, Beck H, et al. Adrenal circadian system in young and elderly human subjects: a comparative study. J Endocr 1982; **93**:201–210.

15 Ottenweller JE, Meier AH, Ferrel BP, Horseman ND, Proctor A. Extrapituitary regulation of the circadian rhythm of plasma corticosteroid concentration in rats. Endocrinology 1978; **103**: 1875–1879.

16 Amirat A, Klammer F, Brudeiux R. Seasonal changes in plasma and adrenal concentration of cortisol, corticosterone, aldosterone and electrolytes in the adult male sand rat / psammomys obesus /. Gen. Comp. Endocrinol. 1980; **40**:36–43.

17 Peschke E, Peschke D, Peil J, Ruzsás Cs, Mess B. Schilddrüsereaktionen der Wistar Ratte in Tagesgang nach Ganglektomie unter Normaltemperatur und Kälteexposition unter Berücksichtigung des Einflusses der Epiphysis cerebri. Acta Histochem 1986; **80**: 63–85.

18 Jorgensen JOL, Moller J, Lauosen T, Orskov JL, Christiansen JS, Weeke J. Growth Hormone administration stimulates energy expediture and conversion of thyroxine to triiodothyronine in a dose dependent manner and suppresses circadian thyrotrophin levels: studies on GH-deficient adults. Clin Endocrinol 1994; **41**: 609–614.

19 Krebietke P. Tageszyklische Schwankungen der Schilddrüsenhormone bei Hänchen / Gallus domesticus/. Untersuchungen des Epithel-Kolloid-Anteils und der Radiojodspeicherung der Schilddrüse, sowie des Radiojodgehaltes des Plasmas. Endokrinologie 1975; **65**:33–41.

20 Prasad L, Thapliyal JP, Chaturvedi CM. The effect of daily injections of L-Dihydroxyphenylalanine and of 5-Hydroxytryptophane in different temporal relationships on thyroid-gonadal interaction in an indian finch, Spotted Munia, Lonchura punctata. Gen Comp Endocrinol 1992; **86**:335–343.

21 Vriend J. Influence of the pineal gland and circadian rhythms in circulating levels of thyroid hormones of male hamsters. J. Pineal Res. 1984; **1**:15–22.

22 Custro N, Scaglione R. Circadian rhythm of TSH in adult man and woman. Acta Endocrinol / Kbh/ 1980; **95**:465–471.

23 Weeke J, Gundersen HJG. Circadian and 30 minutes variations in serum TSH and thyroid hormones in normal subjects. Acta Endocrinol. /Kbh/ 1978; **89**:659–672.

24 Peschke E, Peschke D, Peil J, Mess B. Circannual oscillations of thyroid and cholesterol levels after pinealectomy and gangliectomy related to the weight changes of the pineal, pituitary and thyroid glands. J Pineal Res 1988; **5**:17–20.

25 Reiter RJ. Reproductive effects of the pineal gland and pineal indoles in the Syrian hamster and the albino rat. In. Reiter RJ, ed, The pineal gland. Vol.2. Reproductive effects. CRC. Press Inc Broca Raton, Florida. 1981; p. 45–81.

26 Ghosh M, Haldar C. The avian pineal organ with a special reference to tropical avian pineal organ. PAVO, Ind Journ Ornithol 1995; **32**:1–16.

27 Cockrem JF. Plasma melatonin in the Adelie penguin / Pygoscelis adelie / in continuous day light in Antarctica. J Pineal Res 1991a **10**:2–8.

28 Cockrem J. F. Circadian rhythm of plasma melatonin in the Adelie penguin /Pygoscelis adelie / in constant dim light and artificial photoperiods. J. Pineal Res. 1991b **11**.63–69.

29 Reiter R. J, Rudeen PK, Sackman J. W, Vaughan MK, Johnson LY, Little J. C. Subcutaneous melatonin implants inhibit reproductive atrophy in male hamsters induced by daily melatonin injection. Endocr Res Commun 1977; **4**:35–42.

30 Wolfson A. Light and darkness and circadian rhythms in the regulation of annual reproductive cycles in birds. In. Benoit J. and Assenmacher I. editors La photoregulation de la reproduction chez les oisseaux et les mammiféres.. Colloqu. Internat, Montpellier, CNRS, Paris, 1970; p. 93–119.

31 Mess B, Trentini GP, Tima L. Role of the pineal gland in the regulation of ovulation. Akadémiai Kiadó /Academic Press/, Budapest 1978.

32 Ruzsás Cs, Trentini G. P, Mess B. The role of the pineal gland in the regulation of LH-release in rats with different types of the anovulatory syndrome. Endokrinologie 1977; **70**:142–149.

33 Semm P. The pineal gland and imprinting of the orientation system of migratory birds. In. Trentini GP, De Gaetani C, Pévet P, eds. Fundamentals and Clinics in pineal research. Raven Pres N. Y. 1987; p. 157–160.

34 Schneider T, Thalau HP, Semm P, Wiltschko W. Melatonin is crucial for the migratory orientation of pied flycatchers / Ficedula hypoleuca Pallas/. J Exp Biol 1994; **194**:372–378.

35 Wurtman RJ, Axelrod J, Ficher J. E. Melatonin synthesis in the pineal gland. Effect of light mediated by the sympathetic nervus system. Science 1964; **143**:1328–1336.

36 Moore RY, Heller A, Wurtman R. J, Axelrod J. Visual pathways mediating pineal response to environmental light. Science 1967; **155**:220–223.

37 Mess B, Rékási Z, Csernus V. The use of perifusion technique in the research of pineal neuroendocrinology. The role of different neurotransmitters and neuropeptides in the regulation of pineal hormone secretion. A dynamic in vitro study. In: Fraschini F and Reiter R. J. editors. The role of melatonin and pineal peptides in neruoimmunomodulation. Plenum Press NY 1991; p. 67–77.

38 Mess B, Csernus V, Rékási Z. The role of different neurotransmitters and neuropeptides in the regulation of pineal hormone secretion. A dynamic in vitro study. In. Földes A. and Reiter R. J. editors.. Advances in pineal research, Vol. 6. John Libbey and Co. London, 1991; p.57–66.

39 Rékási Z, Süle N, Csernus V, Mess B. Adrenergic and peptidergic control of the regulation of cAMP efflux and melatonin secretion from perifused rat pineal gland. Endocrine 1998; **9**:89–96.

40 Ghosh M, Csernus V, Mess B. In vitro melatonin secretion pattern of the avian pineal gland with special reference to light reactivity. Neuroendocrinol Lett 1994; **3**:195–200.
41 Csernus V, Ghosh M, Mess B. Development and control of the circadian pacemaker for melatonin release in the chicken pineal gland. Gen Comp Endocrinol 1998; **110**:19–28.
42 Csernus V, Becher P, Mess B. Wavelength dependency of light induced changes in rhythmic melatonin secretion from chicken pineal gland in vitro. Neuroendocrinol Lett 1999; **20**:299–304.
43 Takahashi JS, Hamm H, Menaker M. Circadian rhythms of melatonin release from individual superfused chicken pineal glands in vitro. Proc Natl Acad Sci USA 1980; **77**:2319–2322.
44 Vivien-Roels B, Arendt J. How does the indoleamine of the pineal gland respond to variations of the environment in a non-mammalian vertebrate. Testudo hermanni Gmelin, Psychoneuroendocrinology 1983; **8**:327–332.
45 Underwood H, Harless M. Entrainment of the circadian activity rhythm of lizard to melatonin injections. Physiol Behav 1985; **35**:267–270.
46 Zatz M, Lange G. D, Rollag MD. What does changing temperature do to the melatonin rhythm in cultured chick pineal cells. Am J Physiol 1994; **266**:R50–R58.
47 Barrett R. K, Takahasi J. S. Lability of circadian pacemaker amplitude in chick pineal cells. a temperature-dependent process. J Biol Rhythms 1997; **12**:309–318.
48 Pévet P, Vivien-Roels B, Masson-Pévet M. Low temperature in the golden hamster accelerates the gonadal atrophy induced by short photoperiod but does not affect the daily pattern of melatonin secretion. J. Neural Transm.1989; **76**.119–128.
49 Gwinner E. Circadian and circannual programs in avian migration. J Exp Biol 1996; **199**:39–48.
50 Wiltschko W, Wiltschko R. Orientation in birds. Magnetic orientation and celestial cues in migratory orientation. EXS 1991; **60**: 16–37.
51 Axelrod J, Wurtman R. J. The pineal gland: a biological clock. Problemes Actuels d'Endocrinologie et de Nutrition. 1966; **10**: 201–212.
52 Mess B, Rékási Z, Ghosh M, Csernus V. Regulation of pineal melatonin secretion: comparison between mammals and birds. Acta Biol Hung 1996; **47**:313–322.
53 Reiter R. J. The mammalian pineal gland is an end-organ of the visual system. In: Miles A, Philbrick DRS, Thompson C. editors. Melatonin Clinical perspectives. Oxford Univ. Press, Oxford. 1993; p. 1–42.
54 Rudas P. The role of the suprachiasmatic nuclei in the regulation of biological rhythms. In. Csernus V. and Mess B. editors. Rhythmic biological processes. The role of the biological clocks. Dialog Campus, Budapest, Pécs 2003. p. 93–118.
55 Vigh B, Manzano M. J, Franc C. L, Dávid C, Lukáts A, Szél Á. Changes in the control of the biological circadian rhythms during evolution. The role of the deep brain photorecepors, pineal organs and retina. In. Csernus V. and Mess B. editors. Rhytmic biological processes. The role of the biological clocks. Dialog Campus, Budapest, Pécs 2003. p. 43–92.
56 Oksche A, Kirschstein H. Differences in the elecrtonmicroscopic structure of the sensory cells in the parietal eye and the pineal body / epiphysis cerebri / of Lacertilia. Z Zellforsch 1982; **87**: 159–192.
57 Korf HW. The pineal organ as a component of the biological clock. Phylogenetic and ontogenetic considerations. Ann NY Acad Sci 1994; **719**:13–42.
58 Max M, McKinnon P. J, Seidenman K. J, Barrett R. K, Appleburg M. L, Takahashi JS. et al. Pineal opsin. a non visual opsin expressed in chick pineal. Science, 1995; **267**.1502–1506.
59 Yoshimura T, Suzuki Y, Makino E, Suzuki T, Kuroiwa A, Matsuda Y. et al. Molecular analysis of avian clock genes. Mol Brain Res 2000; **78**.207–215.
60 Liu Y, Heintzen C, Loros J, Dunlap JC. Regulation of clock genes. Cell Mol Life Sci 1999; **55**.1195–1205.
61 Robertson LM, Takahashi JS. Circadian clock in cell culture. I. Oscillation of melatonin release from dissociated chick pineal cells in flow-through microcarrier culture. J Neurosci 1988; **8**: 12–21.
62 Mess B, Csernus V. Rhythmic pineal melatonin production in birds. In. Haldar Ch, Singaravel M, Maitra SK. editors. Treatise on pineal gland and melatonin. USA, Plymouth UK: Science Publisher Inc, Enfield. 2002. p. 177–198.
63 Klein DC, Weller JE. Rapid light induced decrease in the rat serotonin-acetyltransferase activity. Science 1972; **179**:532–533.
64 Reiter RJ, Joshi BN, Heizeller T, Nürnberg F. A single 1 or 5 second light impulse of night inhibits hamster pineal melatonin. Endocrinology 1986; **118**:1906–1909.
65 Vakkuri O, Rintamaki H, Lappäluoto J. Plasma and tissue concentrations of melatonin after midnight light exposure and pinealectomy in the pigeon. J. Endocrinol.1985; **105**.263–268.
66 Ghosh M, Csernus V, Rékási Z, Mess B. Comparative studies on the regulation of pineal melatonin secretion in mammals and birds. In. Haldar Ch. ed The pineal gland. Its Molecular Signals. Recent Res. in Biology, Vol.1.Hindustan Publ. Corporation / India / New Delhi, 1996; p. 5–15.
67 Zatz M. Light and norepinephrine similarly prevent damping of the melatonin rhythm in cultured chick pineal cells: regulation of coupling between pacemaker and overt rhythms. J Biol Rhythms 1991; **6**:137–147.
68 Zatz M, Kasper G, Marguez CR. Vasoactive intestinal peptide stimulates chick pineal melatonin production and interacts with other stimulatory and inhibitory systems but does not show alpha 1-adrenergic potentiation. J Neurochem 1990; **55**: 1149–1153.
69 Simonneaux V, Oichiou A, Pévet P, Masson-Pévet M, Vivien-Roels B, Vaudog H. Kinetic study of melatonin release from rat pineal glands using a perifusion technique. J Pineal Res 1989; **7**: 63–68.
70 Vollrath L. The pineal organ. In. Möllendorf W. F, Bargmann W, Oksche A, Vollrath L. editors. Handbuch der mikroskopischen Berlin: Springer; Anatomie des Menschen. 6/7–665. 1981.