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Human pineal physiology and functional significance of melatonin

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Abstract

Descriptions of the pineal gland date back to antiquity, but its functions in humans are still poorly understood. In both diurnal and nocturnal vertebrates, its main product, the hormone melatonin, is synthesized and released in rhythmic fashion, during the dark portion of the day–night cycle. Melatonin production is controlled by an endogenous circadian timing system and is also suppressed by light. In lower vertebrates, the pineal gland is photosensitive, and is the site of a self-sustaining circadian clock. In mammals, including humans, the gland has lost direct photosensitivity, but responds to light via a multisynaptic pathway that includes a subset of retinal ganglion cells containing the newly discovered photopigment, melanopsin. The mammalian pineal also shows circadian oscillations, but these damp out within a few days in the absence of input from the primary circadian pacemaker in the suprachiasmatic nuclei (SCN). The duration of the nocturnal melatonin secretory episode increases with nighttime duration, thereby providing an internal calendar that regulates seasonal cycles in reproduction and other functions in photoperiodic species. Although humans are not considered photoperiodic, the occurrence of seasonal affective disorder (SAD) and its successful treatment with light suggest that they have retained some photoperiodic responsiveness. In humans, exogenous melatonin has a soporific effect, but only when administered during the day or early evening, when endogenous levels are low. Some types of primary insomnia have been attributed to diminished melatonin production, particularly in the elderly, but evidence of a causal link is still inconclusive. Melatonin administration also has mild hypothermic and hypotensive effects. A role for the pineal in human reproduction was initially hypothesized on the basis of clinical observations on the effects of pineal tumors on sexual development. More recent data showing an association between endogenous melatonin levels and the onset of puberty, as well as observations of elevated melatonin levels in both men and women with hypogonadism and/or infertility are consistent with such a hypothesis, but a regulatory role of melatonin has yet to be established conclusively. A rapidly expanding literature attests to the involvement of melatonin in immune function, with high levels promoting and low levels suppressing a number of immune system parameters. The detection of melatonin receptors in various lymphoid organs and in lymphocytes suggests multiple mechanisms of action. Melatonin has been shown to be a powerful antioxidant, and has oncostatic properties as well, both direct and indirect, the latter mediated by its effects on reproductive hormones. Finally, there are reports of abnormal daily melatonin profiles in a number of psychiatric and neurological disorders, but the significance of such abnormalities is far from clear.

Keywords: Pineal gland; Melatonin; Sleep regulation; Circadian rhythms; Review

1. Introduction

The past 40 years have seen a proliferation of research on the pineal gland and its main product, melatonin. This review focuses on the current state of research on the human pineal, with reference to the non-human literature when appropriate. First, the morphological characteristics of the adult human pineal organ are summarized, drawing on over a century of scientific observations on its anatomy, its connections to the rest of the central nervous system and its extensive vascularization. The secretory mechanisms of the gland are then

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described, with specific emphasis on the synthesis of melatonin and its control by the endogenous timing system. Finally, the physiological significance of melatonin is discussed as it pertains to the well-investigated areas of sleep and temperature regulation, circadian and seasonal rhythmicity, and reproductive physiology, as well as to the relatively less established involvement with the cardiovascular and immune systems, and the complex relationship with psychiatric and neurological disturbances.

2. Historical notes

Identification of the pineal as a distinct cerebral organ has been traced back to the III and IV centuries BC [81,91]. Galen of Pergamon (130–200 AD) appears to have provided the first description of the pineal's location in the human brain, characterizing it as a gland (analogous to lymph glands), and naming it 'konareion' (Latin 'conarium') for its pine cone shape [263]. The organ was subsequently named 'glandula pinealis,' hence 'pineal.' The central location and singularity of the pineal as an unpaired organ, as well as its extensive vascularization, described by Andreas Vesalius Bruxellensis (1515–1564), are probably the foundation of René Descartes' (1596–1650) conceptualization of the pineal as the 'seat of the soul,' or as the organ coordinating psychophysiological functions [1]. The organ has also been called 'cervical body' and 'epiphysis cerebri,' the latter in reference to its position at the top of the brain in many animals. As with other anatomical structures and organs, the various names given to the pineal gland often reflect the contemporary state of knowledge about its structure and functions, which in turn depends on the development of new technologies. For example, advances in microscopy and in histological techniques led to the observation of similarities between the pineal, known as 'the third eye,' and the lateral eyes of lower vertebrates [2], and to the speculation that the mammalian pineal was evolutionarily linked to such photosensory organs [215]. Bioassay advances resulted in the discovery of active pineal "extracts" capable of lightening the color of frog skin [147], leading to the isolation of the pineal hormone melatonin in 1958 [120,121]. Development of fluorescent techniques allowed the measurement of pineal melatonin and serotonin, and the discovery of large day–night variations in their levels [185,186], and of melatonin reduction by exposure to constant light in mice [64].

3. Structure of the mammalian pineal gland

3.1. Gross anatomy

There is a high degree of morphological variability in mammalian pineal organs, both across and within species. Such variability is thought to reflect species-specific adaptive differences in pineal function [50] as well as individual responses to environmental factors (e.g., season of the year and/or time of day). Of the several attempts made at anatomical classification, Vollrath's [232] is the most frequently cited. It is based on the position of the organ relative to the diencephalon and third ventricle, as well as on its shape and size. Thus, a type A pineal rests proximally on the posterior aspect of the diencephalon, while an elongated pineal reaching from the diencephalon to near the cerebellum is a proximo-intermediate-distal (or ABC) type. The human pineal is classified as type A. Its position within 1–2 mm of the midline makes it an ideal reference point for the midsagittal plane. It starts developing in the second month of gestation, as an envagination of the ependyma lining the diencephalic aspect of the third ventricle, between the habenular and posterior commissures, to which it retains a connection (the pineal stalk) composed of a rostral and a caudal lamina. Thus the pineal, surrounded by a pial layer, is suspended in the CFS-filled pineal recess, directly below the splenium (Fig. 1). Average adult dimensions are 5–9 mm in length, 1–5 mm in width, and 3–5 mm in thickness; the average adult weight has been reported as 100–180 mg, with little apparent variation linked to age or gender [6,7,118,253].

3.2. Histology

The human pineal is often described as consisting of a central core composed of lobules and a cortex or periphery with a more diffuse distribution of neurons. The principal cell type of the human pineal parenchyma is the pinealocyte sensu stricto [103]. Human pinealocytes have a prominent nucleus and a granular appearance, with cytoplasmatic processes terminating in peduncula proximal to fenestrated capillaries, a configuration characteristic of endocrine glands (reviewed in [23]). Neuroglia (mostly fibrous astrocytes but also microglia) are unevenly distributed, and usually found surrounding pinealocytes and in peripheral patches [233]. While mammalian pinealocytes are not capable of direct light sensitivity, they retain many characteristics of the true and modified pineal photoreceptors found in anamniotes and in lacertilian and avian species, including immunoreactivity for photoreceptor-specific proteins such as rod-opsin, S-antigen, and recoverin [83,107]. Another similarity with photoreceptors is the concentration of organelles (mitochondria and Golgi complex) in an anucleus region [233]. Calcareous deposits (*acervuli*) are the most distinguishable radiographic characteristic of the pineal. They appear on both parenchymal and intercellular tissue as layered concretions of calcium and magnesium salts, hydroxyapatite, and trace elements. They are thought to be formed by the combination of a polypeptide secreted by the pinealocytes and calcium

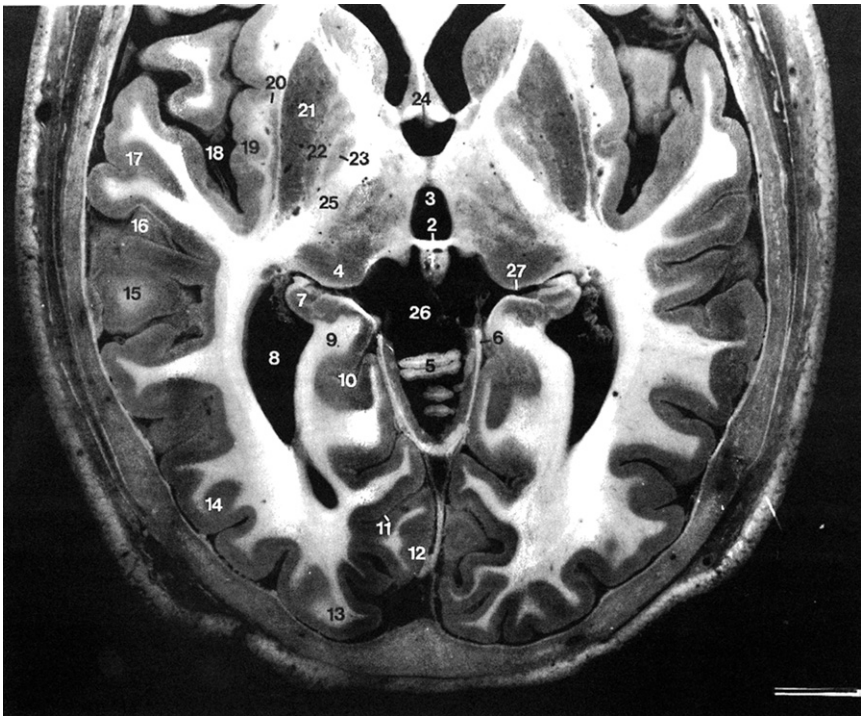

Fig. 1. Axial section of the head with view of the pineal gland. (Reprinted with permission from: Duvernoy et al. [56].) Axial section of the head. Bar = 13 mm. 1, Pineal gland (note its situation in the center of the brain); 2, posterior commissure; 3, third ventricle; 4, pulvinar; 5, superior vermis (culmen); 6, tentorium cerebelli; 7, hippocampus; 8, occipital horn; 9, isthmus; 10, anterior calcarine sulcus; 11, calcarine suscus; 12, cuneus; 13, superior occipital gyrus; 14, middle occipital gyrus; 15, middle temporal gyrus; 16, superior temporal sulcus; 17, superior temporal gyrus; 18, lateral fissure; 19, insula; 20, claustrum; 21, putamen; 22, globus pallidus, pars lateralis; 23, globus pallidus, pars medialis; 24, fornix and anterior commissure; 25, internal capsule, posterior limb. *Subarachnoid cisterns*: 26, quadrigeminal cistern; 27, wing of the ambient cistern (lateral part of the transverse fissure).

accumulated interstitially and intracellularly [136]. Granular calcareous deposits are present since birth, but their density greatly increases with age, leveling off in young adulthood [78]. Radiographic studies have failed to show a correlation between degree of calcification and secretory function [7]. However, calcification density detected by computed tomography can be used to estimate the size of functional tissue, which has been reported to be negatively correlated with age and with the incidence of chronic daytime sleepiness and self-reported sleep disturbances [111,112]. Glial, and less frequently, ependymal benign cysts are often observed, and can lead to morphological and functional degradation of pineal tissue [73,218].

3.3. Vascularization

It has been estimated that in the rat pineal, blood flow (4 ml/min/g) is higher than in any other endocrine gland, excluding the kidney [72]. Indeed, the mammalian pineal, including the human's, is remarkable for its rich vascularization. It receives copious blood supply by branches of the posterior choroidal arteries (including quadrigeminal, thalamic, postero-medial, and postero-lateral branches) deriving from the cerebral arteries that course through the posterior aspect of the mesencephalon [188]. Drainage is into the straight sinus through short-course veins emptying into the internal cerebral veins and basal veins of Rosenthal, which form the great cerebral vein of Galen. Veins and arteries often enter pineal tissue through vascular hila as paired vessels. The extensive internal capillary system is characterized by a network of large and sinusoid capillaries in the septae separating the lobules located at the core of the gland, while the periphery presents fewer and thinner vessels (for an extensive review see [56]). In most mammals, including rats and humans, the pineal is a *circumventricular organ* lacking an endothelial blood–brain barrier, and reacts to peripherally acting drugs.

3.4. Innervation

Peripheral sympathetic and parasympathetic fibers, as well as fibers originating in the central nervous system, innervate the mammalian pineal. Despite being a forebrain structure located close to the midbrain, the pineal differs from other brain structures in receiving relatively scarce afferent innervation from the brain itself. The most important afferents are unmyelinated postganglionic sympathetic fibers originating in the superior cervical ganglia (SCG) and forming the bilateral *nervi conarii* [92], which are thought to course rostrally along the vein

of Galen before entering the pineal posteriorly. Another set of afferents enters the pineal anteriorly through the commissural peduncles, with fibers more numerous in the habenular than in the posterior commissure, and possibly originating in the hypothalamus [233]. A third set of (myelinated) fibers, the 'ventro-lateral pineal tract' has recently been described as arising from the pretectal region, posterior and lateral to the posterior commissure; however, it is not known whether these tracts are pinealofugal or pinealopetal or both [210]. A single unmyelinated afferent tract (midline tract) rising from the rostral tectal area of the brainstem is found in mid-gestational human fetuses, and may be homologous to the nervus pinealis of lower animals [157]. Most nerve terminals are not in direct contact with the pinealocytes, but are found in perivascular spaces and near pinealocyte processes. However, neurotransmission by diffusion through extracellular space is relatively slow, and may not account completely for the rapid physiological response of the pineal to light (see below). In fact, synapse-like contacts between nerve fibers and pinealocytes have also been observed in some species, including non-human primates [87].

3.4.1. Sympathetic innervation

In human and other mammals, the most developed and best studied pineal innervation is the sympathetic noradrenergic (NE) pathway formed by cell bodies located in the paired SCG and reaching the pineal through the nervi conarii. These post-ganglionic neurons receive regulatory input from the suprachiasmatic nucleus (SCN) of the hypothalamus, which in turn receives direct input from retinal ganglion cells [91,92] via the monosynaptic retinohypothalamic tract. Neuropeptide Y (NPY) is colocalized with NE in postganglionic sympathetic fibers in many mammals, and is thought to modulate noradrenergic transmission both pre- and post-synaptically [152,206].

3.4.2. Central, parasympathetic, and peptidergic innervation

There is evidence of *central* nerve fibers entering the human pineal gland through the habenular and posterior commissures and the pineal stalk [91,157]. These fibers have been shown to originate in hypothalamic, limbic forebrain, and visual structures in non-human mammals, and appear to contain various peptides (substance P, vasopressin, oxytocin or neurophysins) in the monkey. It has been suggested that they are analogous to neurosecretory fibers found in the hypophysis [86]. However, to our knowledge the course of these fibers has not been fully traced in humans.

Similarly, *parasympathetic* innervation of the pineal has not been thoroughly investigated in humans. Fibers containing the primary neurotransmitter of parasympathetic neurons, acetylcholine (ACh), have been found in some mammalian species, including the cow and the rat [105,179,247]. The human pineal has a group of interneurons or intrapineal cells [16] which show acetylcholinesterase activity in the monkey [48]. Whether these 'pineal neurons' can be considered true autonomic parasympathetic ganglion cells is controversial [209]. There is some evidence of parasympathetic fibers originating in the mammalian pterygopalatine ganglia and containing vasoactive intestinal peptide (VIP) and other neuropeptides [158]. In humans, there has been speculation that Marburg's and Pastori's ganglia, located outside the pineal parenchyma above and beneath the vein of Galen, may be part of a pineal parasympathetic circuit [158,159,232].

Aside from NPY, which is colocalized with NE in sympathetic fibers, numerous other *peptides* have been found in nerve fibers terminating in perivascular and intraparenchymal areas, including, in non-human primates and other mammals, substance P, vasopressin, oxytocin, and luteinizing hormone releasing hormone [17,197]. It is not known where these peptidergic fibers originate. Experiments in rodents trace VIP-immunoreactive fibers to the pterygopalatine ganglion, the SCG, and the hypothalamic paraventricular nucleus (PVN) [153,201,204]; the PVN also appears to contain the cell bodies of vasopressin and oxytocin fibers found in the pineal, while substance P fibers may originate in the habenula [115]. Neuropeptides may also be expressed by intrapineal cells, which have been shown to be immunoreactive to enkephaline in humans [163].

3.5. Biosynthesis and metabolism of pineal melatonin

The pineal has long been considered a secretory organ, and so-called 'pineal factors' and 'extracts' have been used in both research and clinical settings for over a century [reviewed in 98]. However, it was not until 1958 that one of these 'factors' was isolated and identified in the bovine pineal as the indoleamine *N*-acetyl-5-methoxytryptamine [120,121]. The substance was named 'melatonin' for its ability to affect frog skin melanophores and its chemical relation to serotonin (5-HT, 5-hydroxytryptamine). It is by far the most important and best studied of all pineal products, although several other indoles and peptides are synthesized and secreted by the mammalian pineal gland.

Axelrod [13] demonstrated that the pinealocytes possess all the machinery necessary for the synthesis of melatonin. The biochemical cascade, described by Axelrod [13], Klein et al. [99,100,216] and Reiter [188,189], can be summarized as follows (Fig. 2): pinealocytes take up tryptophan from the blood and convert it to serotonin through hydroxylation and decarboxylation; serotonin is then converted to *N*-acetyl-serotonin by the rate-limiting enzyme *N*-acetyl transferase (NAT); *N*-acetyl-serotonin is methylated into melatonin by the enzyme hydroxyindole-*O*-methyl transferase (HIOMT).

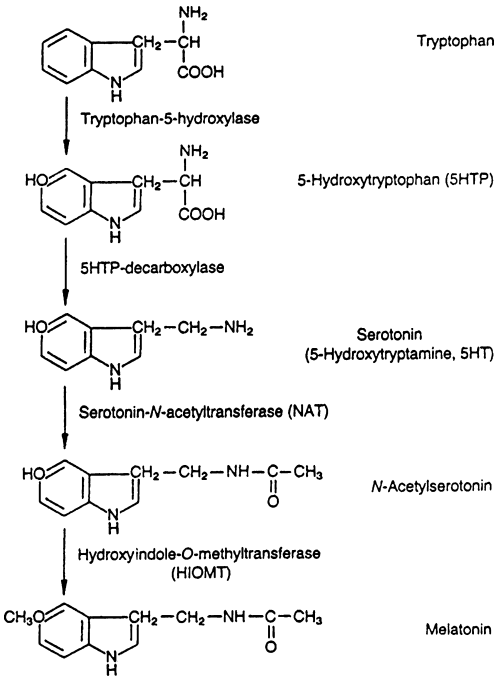

Fig. 2. Chemical structure and synthesis of melatonin. (Reprinted with permission from: Arendt [7].)

Melatonin is a highly lipophilic molecule, as well as having hydrophilic properties; rather than being stored in the secretory organ, upon biosynthesis it is released into capillaries, where up to 70% is bound to albumin [41]. Its half-life in blood after intravenous infusion is about 30 min [144], but a biphasic elimination pattern with half-lives of about 3 and 45 min has also been observed following oral administration [7]. Melatonin is metabolized primarily in the liver but also in the kidney, undergoing hydroxylation and then conjugation into sulfate and glucuronide. Liver and kidney pathologies (e.g., cirrhosis and chronic renal failure) are known to alter clearance rates [112,114,231]. In humans the main metabolite is 6-sulfatoxymelatonin (aMT6s); its urinary concentration accounts for up to 90% of administered melatonin [7].

In addition to blood, saliva, and urine, melatonin has been detected in the CSF of mammals, including primates, where its concentration is much higher than in blood, and in the anterior chamber of the eye, with levels equivalent to those in blood, possibly due to production by the ciliary body [145]. As pointed out by Cagnacci [35], melatonin is also found in many fluids related to reproduction, such as semen, amniotic fluid, and breast milk, as well as in preovulatory follicles. Melatonin levels detected in plasma, CSF, saliva and urine using current techniques are eliminated by pinealectomy, and thus predominantly reflect production by the pineal gland [169]. However, several studies have confirmed the existence of additional sites of melatonin synthesis, including, in humans, the retina, the gut, and bone marrow [35,45]. Thus, melatonin is likely to affect physiological functions by localized action, in addition to its central regulatory function.

Two melatonin receptor subtypes (Mel_{1a} and Mel_{1b}, also called mt1 and MT2) have been identified in humans, based on their binding affinity (picomolar or nanomolar) and chromosomal localization (chromosome 4q35 or 11q21–22) [193]. Mt1 mRNA has been detected in the suprachiasmatic nucleus (SCN) of the hypothalamus, which controls the rhythmic production of melatonin by the pineal gland, as described below [195,242]. Both mt1 and MT2 receptors have been found in the cerebellum [3] and in retinal rods, horizontal amacrine, and ganglion cells [193,202]. In addition, a protein that is 45% identical to the mt1 and MT2 receptors is found in the human hypothalamus and pituitary. It is encoded by a *g-protein* coupled receptor (H9) with an unknown ligand, which was cloned from the human pituitary [194]. Outside of the CNS, human melatonin receptors have been localized in lymphocytes [102,131], in prostate epithelial cells [262], in granulosa cells from preovulatory follicles [256], in spermatozoa [228], in the mucosa/submucosa layer of the colon [183] and in blood platelets [225]. Even in the absence of receptors, the highly diffusible melatonin molecule exerts systemic effects at the most basic cellular level, by modulating cytoskeletal and mitotic functions through binding with calmodulin [19,65], as well as acting as a free-radical scavenger.

Melatonin receptors are widespread in the human fetus (reviewed in [224]), and fetal pinealocytes are capable of melatonin synthesis as early as the 26th week of gestation. However, melatonin levels show no circadian variation and remain unresponsive to light for the first 2–3 months after birth [95,133]. A possible connection has been hypothesized between the onset of melatonin rhythmicity, changes in thermoregulatory control, and sudden infant death syndrome (SIDS), which reaches high levels of prevalence starting around this time [252]. Highest melatonin production occurs during childhood, with a decrease starting around the onset of puberty.

Using radioimmunoassay (RIA) methods, mean melatonin production in healthy adults has been estimated at 28.8 μg/day [113], and at 39.2 and 14.8 μg/night, respectively, in a group of young healthy men and in women in the follicular phase of the menstrual cycle [70]. Similarly, gas chromatography-mass spectrometry techniques have shown slightly lower daily plasma concentrations in women (21.6 μg) than in men (35.7 μg), with constant rates of secretion at night (μg/h: 4.6 in males, 2.8 in females) and no differences related to age [66]. While very stable within individuals [137], the timing, duration and amount of nocturnal melatonin production, show pronounced individual differences, such that very low concentrations may be observed even in healthy, young individuals (low secretors) [9,21]. Pineal

melatonin production is independent of the sleep–wake state [165,234]. Exposure to electromagnetic fields, known to affect rat pineal activity, appears to have little or no effect on human melatonin production [122,203]. Melatonin is, however, affected by exercise [34,160] and by postural changes, with nocturnal plasma and salivary concentrations decreasing when moving from a standing to a supine position and vice-versa [52,108].

3.6. Light–dark and circadian control of melatonin synthesis

The most salient regulatory factor in the production of pineal melatonin is the daily alternation of light and darkness. Melatonin levels are higher at night than during the day in all organisms studied so far, regardless of their rest-activity patterns. In healthy humans, plasma melatonin concentration starts to rise from detectability thresholds (generally = 5 pg/ml) during the evening, reaches maximum levels in the middle of the night and starts decreasing again before habitual wake up time. Under normal diurnal lighting conditions this pattern is very stable across days, and the nocturnal melatonin profile is considered a very reliable phase marker of the endogenous timing system. In the absence of environmental light-dark information (experimentally induced or resulting from blindness), melatonin levels vary with a periodicity slightly different from 24 h (thus 'circadian,' from circa diem). The circadian rhythm of melatonin is endogenously driven, since it persists indefinitely in organisms studied under constant darkness or very dim light. It is abolished by lesions of the SCN [101], indicating that input from the main endogenous circadian pacemaker, located in the SCN, is necessary for its persistence and its synchronization with the external day–night cycle (entrainment).

In addition to its entraining function, photic input has an acute suppressive effect on nocturnal melatonin levels. This suppression is dose-dependent and varies with the spectral characteristics of the light stimulus. Based on inferences from animal research, it was thought initially that only relatively high intensity levels would exert such an inhibitory effect in humans, but several studies have shown that even relatively low light levels, such as those normally encountered indoors, can suppress nocturnal melatonin production [27,128,148] (Fig. 3).

Retinal photic signals reach the SCN through the monosynaptic retinohypothalamic tract (RHT), which originates from a small subset of retinal ganglion cells [150]. In mammals, including humans, these ganglion cells were recently shown to contain a novel photopigment, melanopsin, so named because it was first isolated from frog dermal melanophores [184]. Melanopsin-containing ganglion cells are intrinsically photoreceptive, and are maximally sensitive to short-wavelength light at

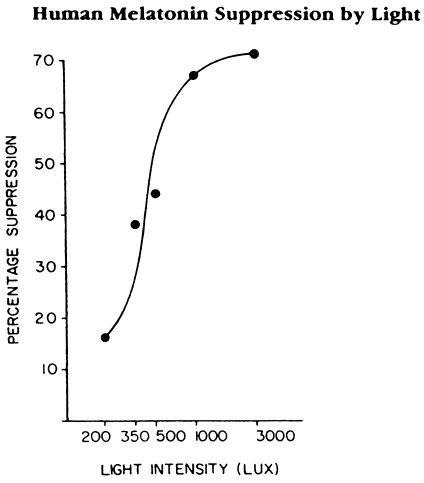

Fig. 3. Maximum percentage suppression of melatonin by light of different intensities: intensity–response curve at 0100 h. (Reprinted with permission from: McIntyre et al. [148].)

484 nm [22]. The fact that light-induced suppression of pineal melatonin output in humans also shows peak sensitivity to short-wavelength light [26,27,223] strongly suggests that melanopsin-containing ganglion cells are involved in the transmission of light input to the pineal. Indeed, animal studies have shown that melanopsin is necessary for several non-image-forming visual functions, including photoentrainment of circadian rhythms, pupillary light reflex, and light-induced melatonin suppression. However, while these functions are disrupted in animals lacking melanopsin, they are not entirely abolished, suggesting that the melanopsin-containing ganglion cells at the origin of the RHT also receive and transmit photic input from the classical photoreceptors, the rods and cones [22].

GABAergic input from the SCN reaches the autonomic parvocellular subdivision of the PVN [90]. Efferents from the PVN go through the medial forebrain bundle and reticular formation and project to the intermediolateral column of the cervical spinal cord (IML), where preganglionic adrenergic fibers then transmit the

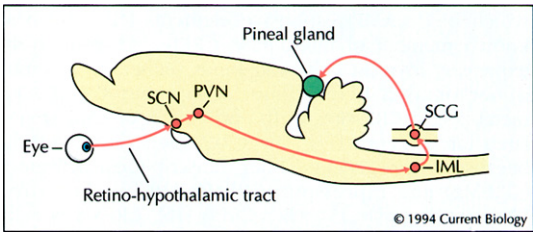

Fig. 4. The neural system regulating pineal *N*-acetyltransferase in the rat. (Reprinted with permission from: Takahashi [217].) Light is detected by the eye, generating a signal that is transmitted by the retino-hypothalamic tract to the suprachiasmatic nucleus (SCN), which contains a circadian clock. The neural pathway includes the paraventricular nucleus (PVN), the intermediolateral cell column (IML), the superior cervical ganglion (SCG), and the pineal gland.

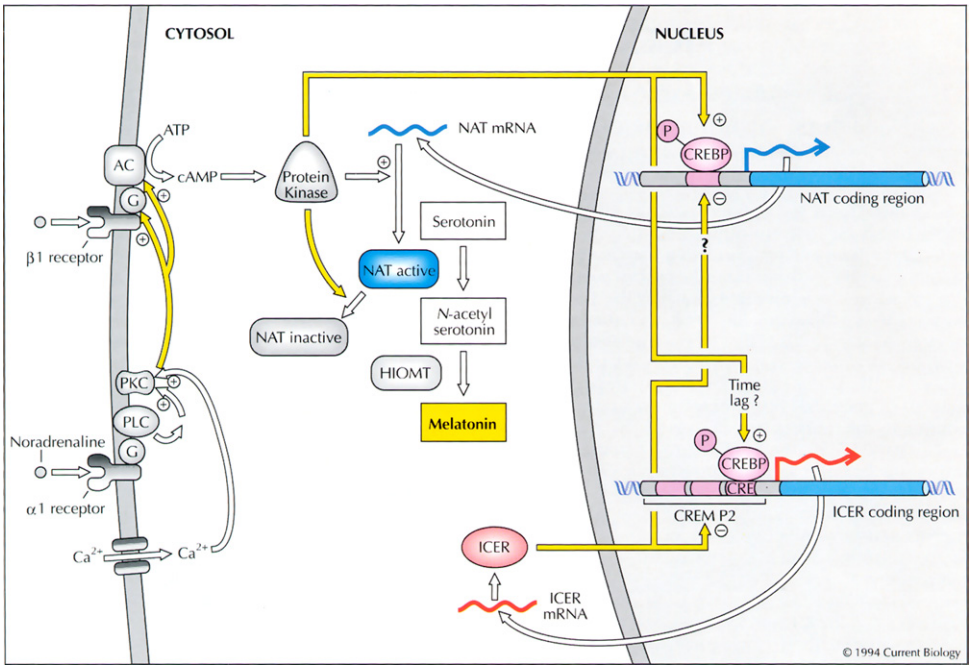

Fig. 5. Adrenergic regulation of melatonin biosynthesis and ICER gene expression in a pineal gland cell. (Reprinted with permission from: Takahashi [217].) AC, adenylate cyclase; G protein; PKC, protein kinase C; PLC, phospholipase C; CRE, cAMP-responsive element; CREBP, CRE-binding protein; NAT, *N*-acetyltransferase; HIOMT, hydroxyindole-*O*-methyltransferase; CREM P2, CREM gene P2 promoter. Yellow arrows indicate interactions.

input to the SCG [162,163]; postganglionic adrenergic fibers reach the pineal from the SCG, and release NE (Fig. 4).

As illustrated in Fig. 5, β-adrenergic receptors on the pinealocytes are activated by a G-protein family subunit, and in turn stimulate production of adenylate cyclase. α_1-Adrenergic receptors potentiate β-adrenergic activity through a sharp increase in Ca^{2+} activity and the activation of protein kinase C (PKC) and prostaglandins [80,109]. Ultimately, synergistic α- and β-adrenergic stimulation results in an elevation of intracellular cAMP, which increases the production of *N*-acetyltransferase (NAT) [99].

In the rat, activation of inducible cAMP early repressor gene (ICER), which can negatively autoregulate, is a control mechanism for limiting nocturnal melatonin production [105,211,217]. There are also suggestions of a parasympathetic regulatory mechanism, based on the observation that rat pinealocytes express all the elements of a glutamatergic system, and that administration of glutamate inhibits NAT activity [164]; in addition, ACh can trigger glutamate microvesicle-mediated exocytosis, and inhibit cAMP-stimulated NE synthesis [106,254].

3.7. Other pineal products and substances

Aside from melatonin, several physiologically active *indoles* are present in the mammalian pineal gland [188], including 5-methoxytryptophol, which exhibits a circadian rhythm parallel to melatonin [250]. However, little research has been done on their synthesis and physiological significance. Aside from the already mentioned classic neurotransmitters and VIP, many other *non-indolic peptides* have been detected in the pineal, and often linked to reproductive function [98]. Some are associated with pineal peptidergic innervation, including vasopressin (VP), oxycitin, VIP, NPY, peptide histidine isoleucine (PHI), calcitonin gene-related peptide (CGRP), substance P, and somatostatin. Pévet [178] has proposed a classification based on whether such peptides are in nerve fibers (class 1), taken up from the circulation (class 2), or synthesized by pinealocytes (class 3). However, no specific peptide has been shown to belong incontrovertibly to one class or another, and possible species-specific differences have not been thoroughly examined [7,106,207]. Hypothalamic and pituitary *hormones* are also present, such as gonadotropin-releasing hormone (GnRH), adrenocorticotropic hormone (ACTH), and prolactin (PRL), among others, and are probably accumulated but not produced by the pineal [106].

4. Role of the pineal gland in human physiology

The pineal exerts its effect on human physiology through a variety of functions: as an endocrine gland, as a transducer, as a regulator of hormones and as a damped circadian oscillator. While the physiological significance of pineal indoles other than melatonin, and of pineal peptides, has not been thoroughly investigated in

humans, melatonin is known or suspected to be involved in mediating all these functions. Extensive animal research has linked pineal melatonin to the expression of seasonal rhythmicity in many mammalian species, to the modulation of circadian rhythms, and to sleep regulation. In addition, reproductive physiology, cardiovascular, and immunological regulation, as well as psychiatric disorders, have been placed under the sphere of influence of this hormone. However, the extent to which results from animal studies can be generalized to humans is often unclear.

4.1. Seasonal cycles

In most vertebrates, seasonal variations in photoperiod duration (daylength) lead to opposite changes in the duration of the nocturnal pineal melatonin secretion. The duration of the melatonin secretory episode thus conveys daylength information, which, in many species, serves to regulate seasonal changes in reproduction, metabolism, and other behavioral and physiological functions [7]. Widespread use of artificial light in modern society means that we are largely shielded from the seasonal changes in daylength. However, it is clear that the human pineal gland has retained the ability to respond to photoperiod duration, although the functional significance of such a mechanism remains uncertain (see extensive review in [245]). Individuals living at high northern latitudes show a lengthening of the nocturnal melatonin peak during winter nights [113]. Similarly, artificial shortening of the natural summer photoperiod results in a lengthening of the melatonin signal [235,236], and exposure to artificial "long nights" in the laboratory is accompanied by an increase in the duration of melatonin production in human subjects [244] (Fig. 6). Additional evidence for the presence of photoperiodic responsiveness in humans is provided by the onset of depressive symptoms with the short days of fall and winter, followed by spontaneous spring–summer remission, characteristic of seasonal affective disorder (SAD) [198]. However, research on the correlation between SAD prevalence rates and latitude, which determines photoperiodic variations, yields conflicting results [151].

4.2. Circadian rhythms

The idea that melatonin acts as an endogenous circadian rhythm synchronizer in mammals [10] is based primarily on data from rodents. Evidence for the role of melatonin in human circadian regulation is based on studies showing phase shifts of circadian rhythms (e.g., in body temperature, endogenous melatonin, and sleep timing) following administration of exogenous melatonin (<5.0 mg). The size and direction of the phase shifts depend on the phase (time of day) of melatonin administration, with phase delays observed following morning administration and phase advances following evening administration [124]. Timed administration of melatonin has been successfully used to facilitate readjustment after acute phase shifts of the light–dark schedule, such as those associated with jet lag and shift work [8]. In most cases, however, it is unclear whether this effect was attributable to the soporific properties of melatonin or to entrainment of the circadian pacemaker responsible for the timing of the sleep–wake rhythm. Some blind individuals have circadian rhythms that cycle independently of

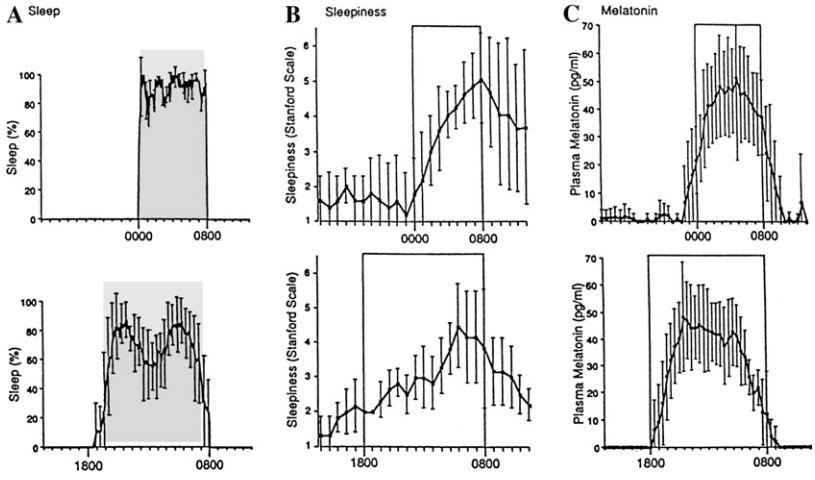

Fig. 6. Duration of the nightly sleep-phase (A), of the nightly rising-phase of sleepiness (B), and of the nightly phase of active MT secretion (C) all expanded when the duration of night was lengthened from 8 (top) to 14 h (bottom). (Reprinted with permission from: Wehr [244].) The average percentage of time asleep during each 6 min (±SD each 30 min) is shown. The dark phase of each photoperiod schedule is indicated by a *shaded rectangle*. Sleepiness and MT levels ere measured on the day following the last night of each photoperiod schedule during a 24-h period (1300–1300) in which the subjects remained continuously awake in constant dim (<1 lux) light. Although no light–dark cycle was applied on the day when these measurements were made, the dark phase of the photoperiod schedule that preceded the measurements is indicated by an *open rectangle*. Of seven men who completed both phases of the experiment, the figure shows data for the six in whom the duration of nocturnal MT secretion lengthened when the photoperiod was shortened.

the light–dark cycle. Melatonin has been reported to be helpful in stabilizing sleep in some such cases [7]. Lewy and colleagues have shown that daily administration of 10 mg melatonin can result in true entrainment of otherwise free-running circadian rhythms (with periods slightly different from 24 h) in eight totally blind individuals, and that in three cases the endogenous melatonin rhythms remained entrained to a 24-h day as the dose was gradually reduced to 0.5 mg/day [125,126,199].

4.3. Sleep

Several lines of research point to a complex web of temporal associations and possible interactions between melatonin, body temperature, and sleep. The evening rise in melatonin secretion, which normally precedes habitual bedtime by about 2 h, is thought to act as a "gating" mechanism for sleep onset [117]. The peak in melatonin production also coincides with the nocturnal trough in body temperature, and there is evidence that the normal nighttime decrease of the body temperature rhythm is partially mediated by the nocturnal rise in endogenous melatonin production [35].

4.3.1. Melatonin and body temperature

Melatonin administration is followed by a decrease in core body temperature and an increase in distal skin temperature, indicating increased heat loss [106]. Similar changes in core and skin temperature also occur at sleep onset, which suggests that the effect of melatonin on sleep may be mediated by thermoregulatory mechanisms [49,108,205]. There are also reports that in healthy men and women the suppression of nocturnal melatonin levels by exposure to bright light is accompanied by an elevation of core body temperature, and that this effect is reversed by administration of exogenous melatonin [37,38,40,214]. The relationship between melatonin, core body temperature and polysomnographic (PSG) sleep parameters was explored in a study by van den Heuvel et al. [226], in which β-adrenergic transmission was blocked by atenolol administration, resulting in the suppression of nocturnal melatonin levels. Atenolol produced a blunting of the nighttime decrease in core body temperature and significant increases in total wake time and wake after sleep onset, at the expense of rapid eye movement (REM) and slow wave sleep. These effects were reversed by administration of 5 mg melatonin. These studies indicate that endogenous melatonin contributes to the nocturnal decrease in body temperature, raising the possibility that nocturnal temperature levels are elevated after pineal resection and may be associated with symptoms of insomnia.

4.3.2. Effects of exogenous melatonin in normal sleepers

The soporific effects of exogenous melatonin in healthy subjects have been extensively documented. Administration of both pharmacological and physiological (usually <0.3 mg) doses during the daytime or early evening, when physiological levels are low, generally increased sleep propensity, subjective sleepiness and fatigue while decreasing sleep latency [55,84,168,180,187,259,260]. In contrast, melatonin administration at night, when endogenous levels are high, had little or no effect in most studies [47,88,213].

4.3.3. Association with insomnia

High melatonin levels throughout the night are thought to promote sleep consolidation, and several investigators have suggested that low nighttime melatonin levels are a causal factor in some types of primary insomnia (e.g., sleep maintenance insomnia). In particular, the increase in sleep complaints and in the use of hypnotic medications with age [53], often accompanied by an increase in the number and duration of wake after sleep onset (WASO), earlier wake-up times, and a decrease in sleep efficiency, has been attributed to the decrease in melatonin production that is frequently found to accompany aging [155,167,258]. More recent data, however, indicate that a reduction in endogenous melatonin production is not a necessary concomitant of aging [258], and that most of the age-related decreases in 6-sulfatoxymelatonin and plasma melatonin levels take place in young adulthood, in the 20–30 year age range [96].

Evidence of a direct relation between endogenous melatonin production and insomnia has been mixed. Some studies report lower melatonin levels in chronic primary insomnia patients than in healthy controls [12,69,74–76,261]. In several other studies, however, melatonin production did not differ between insomniacs and healthy controls, and was not correlated with either actigraphic or PSG-determined sleep parameters [85,138,139,257].

4.3.4. Effects of pinealectomy on sleep

Despite a lack of systematic research, a few published case studies on the sleep of pinealectomized patients suggest that sleep may be negatively affected by abnormally low post-surgical melatonin levels, and that exogenous melatonin administration may be an effective treatment. Etzioni et al. [59] reported the case of a 14-year-old boy with low postoperative serum melatonin levels and complaints of sleep onset and sleep maintenance insomnia both before and during (unsuccessful) chemotherapy; treatment with 3 mg oral melatonin administered before bedtime resulted in a consolidation of nocturnal sleep (Fig. 7). Similarly, Lehmann et al. [119] found disrupted pre- and postoperative sleep–wake cycles in a 24-year-old woman with substantially reduced and arrhythmic melatonin production; nocturnal sleep consolidation was achieved under an 8-week regimen of 2 mg melatonin administered shortly before the desired bedtime.

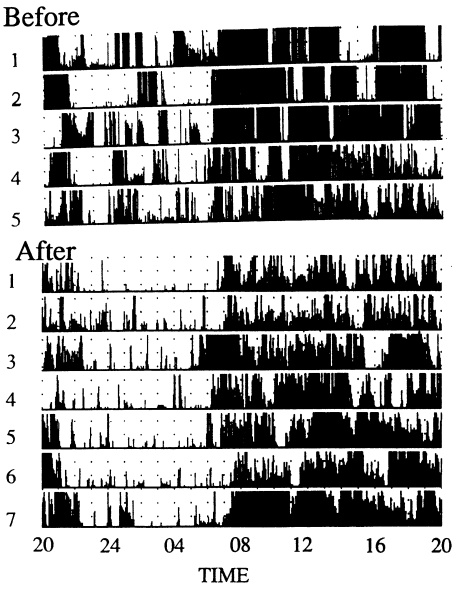

Fig. 7. Sleep fragmentation associated with a pineal neoplasm in a 14-year-old male: actigraphy data (activity in black) for 5 days before and 7 days after treatment with 3 mg melatonin. (Adapted with permission from: Etzioni et al. [59].)

Fast release melatonin and a combination of fast and slow release formulations were also effective in consolidating sleep into a single nocturnal episode in a female patient followed for a period of 4 years after undergoing partial pineal resection [89]. In a study of 12 patients operated for pineal germinoma, Murata et al. [166] identified three patients who reported sleep problems, which were confirmed by polysomnography in two of these patients. Results of a recent survey of 13 adult pineal surgery patients, conducted 6 months to 6.5 years post-surgery, suggest a moderate incidence of sleep and mood disturbance in this clinical population: over half the patients (54%) reported nighttime wake periods lasting 1 h or longer, 31% reported total nighttime sleep durations of less than 6 h, and 38% complained of experiencing poor or disturbed sleep every night. In addition, 58% of the patients reported clinically significant symptoms of depression [140]. However, the extent to which these disturbances are directly attributable to pineal dysfunction rather than to a general effect of brain surgery has yet to be ascertained.

4.4. Reproductive function

A connection between the pineal and human reproductive function was established over a century ago, through clinical observation of the effects of pineal tumors on human sexual development (reviewed in [92,24]). Animals studies, conducted mostly in rodents and in seasonal breeders, have also shown that the duration of the melatonin signal, which depends on the duration of darkness, conveys photoperiodic information that modulates reproductive activity [71,7]). However, the nature of relationship between pineal melatonin and reproductive physiology in humans remains controversial.

It has been suggested that there is a causal relationship between the onset of puberty and the decrease in pineal melatonin production taking place at this developmental stage [11], with the sharpest decline observed between Tanner stages 1 and 5 [241]. Melatonin levels are low in cases of precocious puberty, and decrease after successful treatment of delayed puberty with gonadotropin releasing hormone [239]. However, a correlation between the two variables has not been consistently reported [51,240]. As pointed out by Webb and Puig-Domingo [243] in their review of the literature, the association of melatonin with pubertal development may be the product of maturation of the neuroendocrine–gonadal axis, rather than reflecting a regulatory role of melatonin.

Elevated melatonin levels have been found in women with stress-induced, exercise-induced, or functional hypothalamic hypogonadism [20,21,116], and in men with primary hypogonadism or infertility with oligospermia or azoospermia (Karasek et al., 1990). It has also been reported that melatonin levels are inversely related to estrogens in women with functional amenorrhea [173]. Moreover, administration of exogenous melatonin and synthetic progestagen induces a decrease in LH secretion, blocking ovulation, and the luteal phase increase in progesterone, without affecting FSH or inhibiting estradiol [44,237]. Acute suppression of LH levels has been reported in healthy men as well [134], with a negative correlation between inhibin-β and the LH/testosterone ratio [133]. Inhibition of sperm motility in normal semen has also been observed following melatonin administration in vitro [58]. These findings have prompted a series of ongoing studies on the use of melatonin as a contraceptive.

4.5. Cardiovascular system

There is a well-known diurnal variation in human cardiovascular function, with lower blood pressure, heart rate and cardiac output and higher peripheral vascular resistance at night, when melatonin levels are high, relative to the day [230]. Moreover, there is increased risk of myocardial infraction and stroke in the early morning, coinciding with the fall in melatonin levels [18,67]. Relative to healthy controls, coronary heart disease patients have lower nocturnal melatonin levels in addition to increased NE [31,200].

Early studies in both laboratory animals and humans reported that pineal extracts decreased blood pressure [98], and more recent studies show a hypotensive effect of melatonin in normal, pinealectomized, and spontaneously hypertensive rats [82,94,43]. However, there is also

evidence of an in vitro vasoconstrictive effect of melatonin on rat caudal and cerebral arteries and on pig and human coronary arteries, as well as reduced cerebral blood flow in the rat [143]. In healthy young adults, daytime melatonin administration acutely reduces the pulsatility index of the internal carotid artery, systolic, and diastolic blood pressure and blood NE levels [36,39,4]. Heart rate is also lowered following daytime melatonin administration [77], but it is not affected if melatonin is ingested at the estimated onset of endogenous melatonin production, whereas systolic blood pressure shows an exogenous melatonin-induced decrease at this time [32].

It has been hypothesized that circadian and sympathetic regulation of cardiac function could be mediated by the action of melatonin on the SCN, possibly by affecting release of vasopressin [109,146]. However, when human cardiac parameters are studied in constant conditions by controlling the effects of posture, motor activity and sleep, only heart rate (but not blood pressure) shows an endogenous circadian rhythm [227], as does melatonin, indicating that the daily variations in blood pressure observed during normal routines reflect an effect of sleep. In addition, a distinction has been made between sympathetic and parasympathetic control of cardiovascular parameters, whereby respiratory sinus arrhythmia, an index of parasympathetic activity, appears to be controlled by the circadian system, but preejection period, a measure of sympathetic activity, is probably influenced mostly by sleep [33].

The mechanisms underlying these effects have yet to be elucidated. It is possible that the hypotensive effects of melatonin occur at the peripheral, rather than central, level, or they may result from complex interactions between the two. There is evidence of direct melatonin action on both brain and peripheral blood vessel receptors, but most studies have been conducted on rat caudal artery, that is, on the specialized thermoregulatory organ of a nocturnal animal (reviewed in [110]). As discussed by Cagnacci et al. [39], the mainly vasorelaxant effects of melatonin may result from an effect on NE and other catecholamines, while its vasoconstrictive properties could be associated with a suppression of prostaglandin and nitric oxide, as observed in the rat.

4.6. Immune system and cancer

Research on the involvement of melatonin in immune modulation has proliferated over the past 15 years. For instance, studies by Maestroni and colleagues have shown that suppression of endogenous melatonin in mice results in a decrease in spleen and thymus activity and in primary antibody response to T-dependent antigens, which was reversed by melatonin administration (reviewed in [141]). Additionally, chronic melatonin administration increases T-helper cell activity and IL-2 production [42] and suppresses 5-lypoxigenase gene expression in human lymphocytes [212]. Endogenous melatonin is also thought to regulate production of IL-1 by blood mononuclear cells [68]. In their extensive review Poon and Pang [182] suggest several possible mechanisms of melatonin action on the immune system, based on the detection of melatonin receptors in several lymphoid organs and in lymphocytes. These mechanisms include stimulation of opioid peptides by activated T-helper lymphocytes and of lymphokines (IL2 and γ-interferon), and inhibition of the immunorepressive action of corticosteroids. A well studied mechanism of action is free radical scavenging. Melatonin, which is highly diffusible and may bind to the cell nucleus, has been shown to be a more powerful antioxidant than glutathione, mannitol or vitamin E [190–192].

Animal studies have shown that melatonin has oncostatic properties which may slow down tumor promotion or progression (reviewed in [93]). Pinealectomized rats or hamsters show accelerated growth of transplanted melanoma, Walker 265 carcinoma, Yoshida sarcoma, transplantable leukemia, and mammary tumors, and the effects are reduced by melatonin administration (reviewed in [169]). The oncostatic effect of melatonin is especially pronounced in reproductive-hormone-dependent tumors (breast and ovary), possibly by antagonizing estrogen-mediated mitogenesis [79].

It has also been reported that rats given melatonin together with safrole show a suppression of chemical carcinogen-evoked DNA adduct formation in liver tissue [220,221], suggesting that melatonin may act directly on carcinogenesis in addition to potentiating immune responses. In humans, in vitro studies have shown a dose-dependent inhibitory effect of melatonin on MCF-7 breast cancer lines [25]. However, high doses administered to melanoma patients did not affect survival [196]. Clinical studies inclusive of several tumor types have shown that administration of melatonin with low-dose IL-2 increases the effectiveness of IL-2 in patients that did not tolerate or respond to standard treatments (reviewed in [46]). Similarly, co-administration of melatonin and γ IFN improved tumor regression in metastatic renal cell carcinoma [170].

Maestroni [142] has proposed a dual role of melatonin as an immunomodulator: one is the activation of the immune system following an acute challenge (bacterial or viral infection) by potentiation of Th1 cell activity, macrophage function and cytokine production; the other is a long-term resetting of the circadian modulation of immune functions, affecting hematopoiesis and thymocyte mitosis.

4.7. Psychiatric and neurological disorders

There is an abundance of studies reporting altered melatonin levels in several psychiatric and neurological disorders. Given the complexity of such conditions, very

little can be concluded on the possible functional significance of abnormalities of the melatonin profile. However, any involvement of melatonin is likely to be related to its chronobiotic properties and/or its role in endocrine modulation.

Several studies have reported low nocturnal melatonin levels in *depression*, as well as in dysthymia (reviewed in [29]). However, other well-controlled studies have failed to find significant differences between depressed and healthy subjects [240]. Proponents of the "low melatonin hypothesis" point out correlations between low levels and emotional and cognitive retardation symptoms [248], and suggest a possible association between the onset of seasonal depressive symptoms and a failure to process photoperiodic signals [176]. Such photoperiodic disregulation in SAD patients is more likely to be associated with the phase of the melatonin rhythm relative to the day–night cycle than with its amplitude or absolute level [127]. This possibility is borne out by findings of higher therapeutic responses to bright light exposure in the morning than in the evening [222], although no changes in melatonin profile have been associated with symptom remission [246,251]. On the other hand, treatment of nonseasonal depression with monoamine oxidase (MAO) inhibitors is known to increase melatonin levels by enhancing NAT activity [123], while alprazolam, a 1,4-benzodiazepine analog used in the treatment of anxiety symptoms, suppresses both melatonin and cortisol, possibly by direct action on pineal benzodiazepines receptors [132,149].

Decreased melatonin production has also been documented in *fibromyalgia* [249], which presents some of the neurovegetative symptoms characteristic of depression (e.g., sleep disturbances, fatigue, and muscle pain), while levels in *anorexia nervosa* patients have been reported as elevated or normal, possibly depending on differences in relative weight loss and acute nutritional deficiencies [28,30]. Pathological changes in biological rhythms, including the melatonin rhythm, have been hypothesized in chronic *schizophrenia*, possibly related to a stress-induced degeneration of the hypothalamic–pituitary–adrenal (HPA) axis [62,181]. Medication-free schizophrenics show a blunting of the normal nocturnal melatonin increase, but this pattern is not changed by successful antipsychotic treatment [161].

Anomalies in melatonin production in various neurological conditions and disease states have been extensively documented, and are generally thought to be consequences of the existing disorder, although they may in turn affect the endocrine system and therefore the course of a disease. All pathologies affecting the hypothalamic region (e.g., brainstem degeneration, progressive supranuclear palsy, and midline hematoma) and/or adrenergic function (e.g., multiple system atrophy, upper cervical ganglion injury, spinal chord transection, Shy-Drager syndrome, idiopathic orthostatic hypertension, and diabetic autonomic neuropathy) are likely to result in a disruption of pineal function (reviewed in [177]). Similarly, patients with Cushing's syndrome and with pituitary prolactin- and ACTH-secreting adenomas may present with an abolished melatonin rhythm, while low melatonin levels have been described in cases of acromegaly and prolactinomas. However, most studies report unchanged melatonin production in patients with pituitary tumors (reviewed by Webb and Puig-Domingo [243]), leading to the hypothesis that abolition of melatonin production could result from large invasive lesions of the hypothalamic–pituitary region interrupting the hypothalamic connections to the spinal chord and the SCG, rather than from changes in pituitary hormones [229].

Decreased melatonin levels have been observed following acute ischemic stroke, acute cerebral hemorrhage, and aneurysm rupture, likely due to increased pressure by the third ventricle and altered cerebral artery circulation [63,174,255]. Patients with alcohol-induced CNS damage and Wernicke-Korsakoff syndrome also show blunted nocturnal melatonin levels [249]. There is some evidence that administration of melatonin may reduce epileptic activity in patients with low endogenous melatonin levels [60].

There are some indications of involvement of pineal melatonin in the progression of senile dementia, particularly of the Alzheimer's type, and of a possible therapeutic role of melatonin replacement (reviewed in [175]). Nocturnal melatonin levels were found to be abnormal in Alzheimer's patients relative to healthy elderly, showing reduced amplitude, larger variability in peak times and diminished total secretion. Lower melatonin levels were associated with increased fragmentation of the rest-activity rhythm [156] and with immunological alterations [61]. In a postmortem study, melatonin concentrations in ventricular CSF of Alzheimer's patients were found to be only one-fifth of those of elderly controls, with no difference between presenile and senile diagnosis [130] Diurnal plasma melatonin levels of Alzheimer's patients were reported to be higher than those of psychiatric patients, and did not appear to be affected by exposure to bright light, possibly indicating altered light sensitivity in these patients [172]. A study of the effects of donezepil, a cholinesterase inhibitor, showed diurnal variations in urinary 6-sulfatoxymelatonin levels in 50% of healthy elderly, 20% of patients with untreated Alzheimer's, and 67% of Alzheimer's patients treated with donezepil. However, total daily levels were not affected by treatment, and were not significantly different between elderly controls and Alzheimer's patients [135]. Amyloid-β-peptides aggregate spontaneously in vitro, forming amyloid fibrils, and are known to play a role in the progressive neurodegeneration characteristic of Alzheimer's disease. Several in vitro investigations have shown that administration of melatonin inhibits the formation of β-sheet or amyloid fibrils (reviewed in [208]).

4.8. Pineal neoplasms

The role of melatonin in patients with pineal tumors has not been well defined [5,14,15,104,154,238]. Curiously, altered melatonin levels have been seen in patients with other intracranial or systemic malignancies but their significance is unknown [54,57,129,219,229]. Some case studies and anecdotal reports suggest that melatonin levels may be important as a diagnostic marker or as a measure of tumor removal, but such evidence has been inconsistent [5,14,15,97,171,238]. Melatonin may be secreted by pineal tumors, particularly pineal cell tumors, and its circadian secretory pattern may be altered by any mass lesion in the pineal gland. Likewise, whether or not absence of melatonin is an indicator of the extent of pineal tumor removal has not been substantiated [154,238]. More sensitive assays may determine some residual melatonin secretion or it may be an indicator of secretory capacity of other sources of melatonin outside of the pineal gland.

5. Conclusions

The vast amount of research conducted on the mammalian pineal over the past 40 years or so has led to great progress in understanding its morphology and in characterizing its mechanisms of action, but has not been accompanied by a parallel clarification of its physiological significance, least of all in humans, despite notable progress in understanding its functions in human circadian rhythmicity and in sleep and temperature regulation. A few years ago one of the groups of researchers most responsible for advancing knowledge of this gland concluded that "there is no good evidence for a major physiological role of the human pineal gland," and pointed out that most studies of pineal function were limited to the effects of melatonin, to the exclusion of other pineal indoles and peptides [6, pp. 267–268]. Some developments have occurred since these comments that point to the existence of a systemic and diffuse modulatory action of pineal products, rather than a strictly regulatory one, involving the reproductive, cardiovascular and immune systems. Our ability to define physiological abnormalities now starts at the molecular level, and allows us to observe the contribution of the pineal and its products to a chain of biological events culminating in phenomena that may ultimately show no direct relationship to the pineal itself. Whether the pineal is directly or indirectly regulating or modulating certain physiological processes may also be completely distinct from the therapeutic potentials of melatonin, which show some promise and should continue to be carefully examined.

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References

[1] C. Adam, P. Tannery, Oeuvres de Descartes, vol. XI, Librairie Philosophique J. Vrinn, Paris, 1974.
[2] F. Ahlborn, Ueber die Bedeutung der Zirbeldrüse (Glandula pinealis; Conarium; Epiphysis cerebri), Zschr wiss Zool. 40 (1884) 331–337.
[3] W.M. Al-Ghoul, M.D. Herman, M.L. Dubocovich, Melatonin receptor subtype expression in human cerebellum, Neuroreport 9 (1998) 4063–4068.
[4] S. Arangino, A. Cagnacci, M. Angiolucci, A.M. Vacca, G. Longu, A. Volpe, G.B. Melis, Effects of melatonin on vascular reactivity, catecholamine levels, and blood pressure in healthy men, Am. J. Cardiol. 83 (1999) 1417–1419.
[5] J. Arendt, Melatonin as a tumour marker in a patient with pineal tumour, Br. Med. J. 26 (1978) 635–636.
[6] J. Arendt, Mammalian pineal rhythms, Pineal Res. Rev. 3 (1985) 161–213.
[7] J. Arendt, Melatonin and the Mammalian Pineal Gland, Chapman & Hall, London, 1995.
[8] J. Arendt, D.J. Skene, B. Middleton, S.W. Lockley, S. Deacon, Efficacy of melatonin treatment in jet lag, shift work, and blindness, J. Biol. Rhythms 12 (1997) 604–617.
[9] J. Arendt, A. Wirz-Justice, J. Bradtke, M. Kornemark, Long-term studies on immunoreactive human melatonin, Ann. Clin. Biochem. 16 (1979) 307–312.
[10] S.M. Armstrong, Melatonin: the internal zeitgeber of mammals, Pineal Res. 7 (1989) 157–202.
[11] A. Attanasio, F. Borrelli, D. Gupta, Circadian rhythms in serum melatonin from infancy to adolescence, J. Clin. Endocrinol. Metab. 61 (1985) 388–390.
[12] M.E. Attenburrow, P.J. Cowen, A.L. Sharpley, Low dose melatonin improves sleep in healthy middle-aged subjects, Psychopharmacology 126 (1996) 179–181.
[13] J. Axelrod, The pineal gland: a neurochemical transducer, Science 1184 (1974) 1341–1348.
[14] S.G. Barber, J.A. Smith, R.C. Hughes, Melatonin as a tumour marker in a patient with pineal tumour, Br. Med. J. 2 (6133) (1978) 328.
[15] S.G. Barber, J.A. Smith, D.H. Cove, S.C. Smith, D.R. London, Marker for pineal tumours?, Lancet 2 (8085) (1978) 372–373.
[16] W. Bargmann, Neurosecretion, Int. Rev. Cytol. 19 (1966) 183–201.
[17] J. Barry, Immunofluorescence study of the preoptico-terminal LHRH tract in the female squirrel Monkey during the estrous cycle, Cell Tissue Res. 198 (1979) 1–13.
[18] S. Behar, H. Reicher-Reiss, M. Zion, E. Kaplinsky, L. Mandelzweig, U. Goldbourt, Circadian variation and possible external triggers of onset of myocardial infraction. SPRINT Study Group, Am. J. Med. 94 (1993) 395–400.
[19] G. Benitez-King, Calmodulin mediates melatonin cytoskeletal effects, Experientia 49 (1993) 635–641.
[20] S.L. Berga, S.S.C. Yen, Amplification of nocturnal melatonin secretion in women with functional hypothalamic amenorrhea, J. Clin. Endocrinol. Metab. 66 (1988) 242–244.
[21] J.-D. Bergiannaki, T.J. Paparrigopoulos, M. Syrengela, C.N. Stefanis, Low and high melatonin excretors among healthy individuals, J. Pineal Res. 18 (1995) 159–164.

[22] D.M. Berson, Strange vision: ganglion cells as circadian photoreceptors, Trends Neurosci. 26 (2003) 314–320.
[23] K.P. Bhatnagar, The ultrastructure of mammalian pinealocytes: a systematic investigation, Microsc. Res. Tech. 21 (1992) 85–115.
[24] S. Binkley, The Pineal: Endocrine and Nonendocrine Function, Prentice Hall, Englewood Cliffs, NJ, 1988.
[25] D.E. Blask, S.T. Wilson, Breast cancer: a model system for studying the neuroendocrine role of pineal melatonin in oncology, Biochem. Soc. Trans. 20 (1992) 309–311.
[26] G.C. Brainard, M. Menaker, R.H. Frederickson, S.T. Miller, R.G. Weleber, V. Cassone, D. Hudson, Dose–response relationship between light irradiance and the suppression of plasma melatonin in human volunteers, Brain Res. 454 (1988) 212–218.
[27] G.C. Brainard, J.P. Hanifin, J.M. Greeson, B. Byrne, G. Glickman, E. Gerner, M.D. Rollag, Action spectrum for melatonin regulation in humans: evidence for a novel circadian photoreceptor, J. Neurosci. 21 (2001) 6405–6412.
[28] A. Brezinski, H.H. Lynch, M.M. Seibel, M.H. Deng, T.M. Nader, R.J. Wurtman, Circadian rhythm of plasma melatonin during the normal menstrual cycle and in amenorrheic women, J. Clin. Endocrinol. Metab. 66 (1988) 891–895.
[29] G.M. Brown, Melatonin in psychiatric and sleep disorders: therapeutic implications, CNS Drugs 3 (1995) 209–226.
[30] G.M. Brown, Pineal function in psychiatric disorders, in: P.L. Tang, S.F. Pang, R.J. Reiter (Eds.), Melatonin: A Universal Photoperiodic Signal with Diverse Actions, Front Horm. Res., vol. 21, Karger, Basel, 1996, pp. 174–179.
[31] P. Brugger, M. Herold, Impaired nocturnal secretion of melatonin in coronary heart disease, Lancet 345 (1995) 1408.
[32] H.J. Burgess, S. Savic, S.S. Gilbert, D. Dawson, Effects of bright light and melatonin on sleep propensity, temperature, and cardiac activity at night, J. Appl. Physiol. 91 (2001) 1214–1222.
[33] H.J. Burgess, Y. Kim, D. Luke, Sleep and circadian influences on cardiac autonomic nervous system activity, Am. J. Physiol. 42 (1997) H1761–H1768.
[34] O.M. Buxton, M. L'Hermite-Baleriaux, U. Hirschfeld, E. Cauter, Acute and delayed effects of exercise on human melatonin secretion, J. Biol. Rhythms 12 (1997) 568–574.
[35] A. Cagnacci, Melatonin in relation to physiology in adult humans, J. Pineal Res. 21 (1996) 200–213.
[36] A. Cagnacci, S. Arangino, M. Angiolucci, E. Maschio, G. Longu, G.B. Melis, Potentially beneficial cardiovascular effects of melatonin administration in women, J. Pineal Res. 22 (1997) 16–19.
[37] A. Cagnacci, J.A. Elliott, S.S.C. Yen, Melatonin: a major regulator of the circadian rhythm of core body temperature in humans, J. Clin. Endocrinol. Metab. 74 (1992) 447–452.
[38] A. Cagnacci, R. Soldani, S.S.C. Yen, The effect of light on core body temperature is mediated by melatonin in women, J. Clin. Endocrinol. Metab. 76 (1993) 1036–1038.
[39] A. Cagnacci, S. Arangino, M. Angiolucci, E. Maschio, G.B. Melis, Influences of melatonin administration on the circulation of women, Am. J. Physiol. 274 (1998) R335–R338.
[40] A. Cagnacci, R. Soldani, G.A. Laughlin, S.S.C. Yen, Modification of circadian body temperature rhythm during the luteal menstrual phase: role of melatonin, J. Appl. Physiol. 80 (1996) 25–29.
[41] D.P. Cardinali, H.J. Lynch, R.J. Wurtman, Binding of melatonin to human and rat plasma proteins, Endocrinology 91 (1972) 1213–1218.
[42] M.C. Caroleo, D. Frasca, G. Nistico, G. Doria, Melatonin as immunomodulator in immunodeficient mice, Immunopharmacology 23 (1992) 81–89.
[43] J.I. Chuang, S.S. Chen, M.T. Lin, Melatonin decreases brain serotonin release, arterial pressure and heart rate in rats, Pharmacology 47 (1993) 91–97.
[44] M. Cohen, A.M. van Heusden, H.E.R. Verdonk, P. Wijnhamer, Melatonin/norethisterone contraception, in: Y. Touitou, P. Pevet (Eds.), Melatonin and the Pineal Gland: From Basic Sciences to Clinical Applications, Excerpta Medica, Amsterdam, 1993, pp. 339–345.
[45] A. Conti, S. Conconi, E. Hertens, K. Skwarlo-Sonta, M. Markowska, G.J.M. Maestroni, Evidence for melatonin synthesis in mouse and human bone marrow cells, J. Pineal Res. 28 (2000) 193–202.
[46] A. Conti, G.J.M. Maestroni, The clinical neuroimmunotherapeutic role of melatonin in oncology, J. Pineal Res. 19 (1995) 103–110.
[47] H. Cramer, J. Rudolph, U. Consbruch, K. Kendel, On the effects of melatonin on sleep and behavior in man, Adv. Biochem. Psychopharmacol. 11 (1974) 187–191.
[48] G.F.X. David, T.C.A. Kumar, Histochemical localization of cholinesterase in the neural tissue of the pineal in the rhesus monkey, Experientia 34 (1978) 1067–1068.
[49] D. Dawson, N. Encel, Melatonin and sleep in humans, J. Pineal Res. 15 (1993) 1–12.
[50] D. Dawson, C.J. van den Heuvel, Integrating the actions of melatonin on human physiology, Ann. Med. 30 (1998) 95–102.
[51] A. de Leiva, F. Tortosa, M.A. Peinado, J. Serrano, J. Rodrîguez-Espinosa, M. Puig-Domingo, Episodic nyctohemeral secretion of melatonin in adult humans: lack of relation with LH pulsatile pattern, Acta Endocrinol. (Copenh.) 122 (1990) 76–82.
[52] S. Deacon, J. Arendt, Posture influences melatonin concentrations in plasma and saliva in humans, Neurosci. Lett. 167 (1994) 191–194.
[53] W.C. Dement, L.E. Miles, M.A. Carskadon, White paper on sleep and aging, J. Am. Geriatr. Soc. 30 (1982) 25–30.
[54] R. Dempsey, W. Chandler, Abnormal serum melatonin levels in patients with intrasellar tumors, Neurosurgery 15 (1984) 815–819.
[55] A.B. Dollins, H.J. Lynch, R.J. Wurtman, M.H. Deng, K.U. Kischka, R.E. Gleason, H.R. Lieberman, Effect of pharmacological daytime doses of melatonin on human mood and performance, Psychopharmacology 112 (1993) 490–496.
[56] H.M. Duvernoy, B. Parratte, L. Tatou, F. Vuillier, The human pineal gland. Relationships with surrounding structures and blood supply, Neurol. Res. 22 (2000) 747–790.
[57] S. Erlich, M. Apuzzo, The pineal gland: anatomy, physiology and clinical significance, J. Neurosurg. 63 (1985) 321–341.
[58] E. Ertungealp, Effects of indoleamines on sperm motility in vitro, Hum. Reprod. 7 (1992) 987–990.
[59] A. Etzioni, R. Luboshitzky, D. Tiosano, M. Ben-Harush, D. Goldsher, P. Lavie, Melatonin replacement corrects sleep disturbances in a child with pineal tumor, Neurology 46 (1996) 262–263.
[60] J.D. Fauteck, J. Bockmann, T.M. Bockers, W. Wittkowski, R. Kohling, A. Lucke, H. Straub, E.J. Speckmann, I. Tuxhorn, P. Wolf, Melatonin reduces low-Mg^{2+} epileptiform activity in human temporal slices, Exp. Brain Res. 107 (1995) 321–325.
[61] E. Ferrari, M. Fioravanti, F. Magri, S.B. Solerte, Variability of the interactions between neuroendocrine and immunological functions in physiological aging and dementia of the Alzheimer's type, Ann. N. Y. Acad. Sci. 917 (2000) 582–596.
[62] I.N. Ferrier, J. Arendt, E.C. Johnstone, T.J. Crow, Reduced nocturnal melatonin secretion in chronic schizophrenia: relationship to body weight, Clin. Endocrinol. 17 (1982) 181–187.
[63] P. Fiorina, G. Lattuada, O. Ponari, C. Silvestrini, P. DallAglio, Impaired nocturnal melatonin excretion and changes of immunological status in ischaemic stroke patients, Lancet 347 (1996) 692–693.
[64] V. Fiske, Discovery of the relation between light and pineal function, in: M. Altschule (Ed.), Frontiers of Pineal Physiology, MIT Press, Cambridge, MA, 1975, pp. 5–11.
[65] O. Fjaerli, T. Lund, B. Osterud, The effect of melatonin on cellular activation processes in human blood, J. Pineal Res. 26 (1999) 50–55.

[66] J.B. Fourtillan, M. Brisson, M. Fourtillan, I. Ingrand, J.P. Decourt, J. Girault, Melatonin secretion occurs at a constant rate in both young and older men and women, Am. J. Physiol. Endocrinol. Metab. 280 (2001) E11–E22.
[67] M. Gallerani, R. Manfredini, L. Ricci, A. Coccorullo, C. Goldoni, M. Bigoni, C. Fersini, Chronobiological aspects of acute cerebrovascular diseases, Acta Neurol. Scand. 87 (1993) 482–487.
[68] S. Garcia-Maurino, M.G. Gonzalez-Haba, J.R. Calvo, R. Goberna, J.M. Guerrero, Involvement of nuclear binding sites for melatonin in the regulation of IL-2 and IL-6 production by human blood mononuclear cells, J. Neuroimmunol. 92 (1998) 76–84.
[69] D. Garfinkel, M. Laudon, D. Nof, N. Zisapel, Improvement of sleep quality in elderly people by controlled-release melatonin, Lancet 346 (1995) 541–544.
[70] M. Geoffriau, B. Claustrat, J. Veldhuis, Estimation of nocturnal melatonin production in humans by deconvolution analysis, in: Y. Touitou (Ed.), Biological Clocks, Mechanisms and Applications, Elsevier, Amsterdam, 1998, pp. 325–328.
[71] B.D. Goldman, J.A. Elliott, Photoperiodism and seasonality in hamsters: role of the pineal gland, in: M.H. Stetson (Ed.), Processing of Environmental Information in Vertebrates, Springer Verlag, New York, 1988, pp. 203–218.
[72] H. Goldman, R.J. Wurtman, Flow of blood to the pineal body of the rat, Nature 203 (1964) 27–88.
[73] J. Golzarian, D. Baleriaux, W.O. Bank, C. Matos, J. Flament-Durand, Pineal cyst: normal or pathological, Neuroradiology 35 (1993) 251–253.
[74] I. Haimov, M. Laudon, N. Zisapel, M. Souroujon, D. Nof, A. Shlitner, P. Herer, O. Tzischinsky, P. Lavie, Sleep disorders and melatonin rhythms in elderly people, Br. Med. J. 309 (1994) 167.
[75] I. Haimov, P. Lavie, M. Laudon, P. Herer, C. Vigder, N. Zisapel, Melatonin replacement therapy of elderly insomniacs, Sleep 18 (1995) 598–603.
[76] G. Hajak, A. Rodenbeck, J. Staedt, B. Bandelow, G. Huether, E. Rüther, Nocturnal plasma melatonin in patients suffering from chronic primary insomnia, J. Pineal Res. 19 (1995) 116–122.
[77] A.S. Harris, H.J. Burgess, D. Dawson, The effects of day-time exogenous melatonin administration on cardiac autonomic activity, J. Pineal Res. 31 (2001) 199–205.
[78] V.K. Helmke, P. Winkler, Die häufigkeit von penealisverkalkungen in den ersten 18 lebensjahren, Fortschr. Rontgenstr. 144 (1986) 221–226.
[79] S.M. Hill, L.L. Spriggs, M.A. Simon, H. Muraoka, D.E. Blask, The growth inhibitory action of melatonin on human breast cancer cells is linked to the estrogen response system, Cancer Lett. 64 (1992) 249–256.
[80] A.K. Ho, C.L. Chik, D.C. Klein, Protein kinase C is involved in adrenergic stimulation of pineal cGMP accumulation, J. Biol. Chem. 262 (1987) 10059–10064.
[81] R. Hoffman, R.J. Reiter, Pineal gland: influence on gonads of male hamsters, Science 148 (1965) 1609–1611.
[82] S.W. Holmes, D. Sugden, The effect of melatonin on pinealectomy-induced hypertension in the rat, Br. J. Pharmacol. 56 (1976) 360P.
[83] S.K. Huang, D.C. Klein, H.-W. Jofr, Immunocytochemical demonstration of rod-opsin, S-antigen, and neuron-specific proteins in the human pineal gland, Cell Tissue Res. 267 (1992) 493–498.
[84] R.J. Hughes, P. Badia, Sleep-promoting and hypothermic effects of daytime melatonin administration in humans, Sleep 20 (1997) 124–131.
[85] R.J. Hughes, R.L. Sack, A.J. Lewy, The role of melatonin and circadian phase in age-related sleep-maintenance insomnia: assessment in a clinical trial of melatonin replacement, Sleep 21 (1998) 52–68.
[86] T. Ichimura, The ultrastructure of neurona; -pinealocyteic interconnections in the monkey pineal, Microsc. Res. Tech. 21 (1992) 124–135.
[87] T. Ichimura, T. Arikuni, P.H. Hashimoto, Fine structural study of the pineal body of the monkey (*Macaca fuscata*) with special reference to synaptic formations, Cell Tissue Res. 244 (1986) 569–576.
[88] S.P. James, W.B. Mendelson, D.A. Sack, N.E. Rosenthal, T.A. Wehr, The effect of melatonin on normal sleep, Neuropsychopharmacology 1 (1987) 41–44.
[89] J.E. Jan, J. Tai, G. Hahn, R.R. Rothstein, Melatonin replacement therapy in a child with a pineal tumor, J. Child Neurol. 162 (2001) 139–140.
[90] A. Kalsbeek, M.-L. Garidou, I.F. Palm, J. van der Vliet, V. Simonneaux, P. Pévet, R.M. Buijs, Melatonin sees the light: blocking GABA-ergic transmission in the paraventricular nucleus induces daytime secretion of melatonin, Eur. J. Neurosci. 12 (2000) 3146–3154.
[91] J.A. Kappers, The development, topographical relations and innervation of the epiphysis cerebri in the albino rat, Z. Zellforsch. 52 (1960) 163–215.
[92] J.A. Kappers, Short history of pineal discovery and research, in: The Pineal Gland of Vertebrates including Man, in: J.E. Kappers, P. Pevét (Eds.), Progr. Brain Res., vol. 52, Elsevier, Amsterdam, 1979, pp. 3–22.
[93] M. Karasek, M. Pawlikowski, Antiproliferative effects of melatonin and CGP 52608, Biol. Signals Recept. 8 (1999) 75–78.
[94] K. Kawashima, Y. Miwa, K. Fujimoto, H. Ochata, N. Nishino, H. Koike, Antihypertensive action of melatonin in the spontaneously hypertensive rat, Clin. Exp. Hypertens. Ther. Pract. A 9 (1987) 1121–1131.
[95] D.J. Kennaway, F.C. Gable, G.E. Stamp, Factors influencing the development of melatonin rhythmicity, J. Clin. Endocrinol. Metab. 81 (1998) 1525–1532.
[96] D.J. Kennaway, K. Lushington, D. Dawson, L. Lack, C. van den Heuvel, N. Rogers, Urinary 6-sulfatoxymelatonin excretion and aging: new results and a critical review of the literature, J. Pineal Res. 27 (1999) 210–220.
[97] D.J. Kennaway, G. McCulloch, C.D. Matthews, R.F. Seamark, Plasma melatonin, luteinizing hormone, follicle-stimulating hormone, prolactin, and corticoids in two patients with pinealoma, J. Clin. Endocrinol. Metab. 9 (1979) 144–145.
[98] J.I. Kitay, M.D. Altschule, The Pineal Gland. A review of the physiologic literature, Harvard University Press, Cambridge, MA, 1995.
[99] D.C. Klein, Photoneural regulation of the mammalian pineal gland, in: D. Evered, S. Clark (Eds.), Photoperiodism, Melatonin and the Pineal, Ciba Foundation Symposium, vol. 117, Pitman, London, 1985, pp. 38–56.
[100] D.C. Klein, S.L. Coon, P.H. Roseboom, J.L. Weller, M. Bernard, J.A. Gastel, M. Zatz, M. Iubone, I.R. Rodriguez, V. Begay, J. Falcon, G. Cahill, V.M. Cassone, R. Baler, The melatonin rhythm generating enzyme: molecular regulation of serotonin *N*-acetyltransferase in the pineal gland, Rec. Progr. Hormone Res. 52 (1997) 307–358.
[101] D.C. Klein, R.Y. Moore, Pineal *N*-acetyltransferase and hydroxyindole-*O*-methyltransferase: control by the retinohypothalamic tract and the suprachiasmatic nucleus, Brain Res. 174 (1979) 245–262.
[102] R. Konachkieva, S. Kyirkchiev, I. Kekhayov, P. Taushanova, L. Kanchev, Selective effect of methoxyindoles on the lymphocyte proliferation and melatonin binding to activated human lymphoid cell, J. Neuroimmunol. 63 (1995) 125–132.
[103] H.-W. Korf, Evolution of melatonin-producing pinealocytes, in: J. Olcese (Ed.), Melatonin after Four Decades, Kluwer Academic/Plenum Press, New York, 2000, pp. 17–29.

[104] H.-W. Korf, J.N. Bruce, B. Vistica, M. Rollag, B.M. Stein, D.C. Klein, Immunoreactive S-antigen in cerebrospinal fluid: a marker of pineal parenchymal tumors, J. Neurosurg. 70 (1989) 682–687.
[105] H.-W. Korf, C. Schomerus, E. Maronde, J.H. Stehle, Signal transduction molecules in the rat pineal organ: CA^{2+}, pCREB, and ICER, Naturrwissenschaften 83 (1996) 535–543.
[106] H.-W. Korf, C. Schomerus, J.H. Sthele, The Pineal Organ, Its Hormone Melatonin, and the Photoneuroendocrine System, Springer, Berlin, 1998.
[107] H.-W. Korf, B.H. White, D.C. Schaad, D.C. Klein, Recoverin in pineal organs and retinae of various vertebrate species including man, Brain Res. 595 (1992) 57–66.
[108] K. Kräuchi, C. Cajochen, A. Wirz-Justice, A relationship between heat loss and sleepiness: effects of postural change and melatonin administration, J. Appl. Physiol. 83 (1997) 134–139.
[109] D.N. Krause, M.L. Dubokovich, Regulatory sites in the melatonin system of mammals, Trends Neurosci. 13 (1990) 464–470.
[110] D.N. Krause, G.G. Geary, S. Doolen, S.P. Duckles, Melatonin and cardiovascular function, in: J. Olcese (Ed.), Melatonin after Four Decades, Kluwer Academic/Plenum Press, New York, 2000, pp. 299–310.
[111] D. Kunz, F. Bes, P. Schlattann, W.M. Herrmann, On pineal calcification and its relation to subjective sleep perception: a hypothesis driven study, Psychiatry Res. 82 (1998) 187–191.
[112] D. Kunz, S. Schmitz, R. Mahlberg, A. Mohr, C. Stöter, K.-J. Wolf, W.M. Herrmann, A new concept for melatonin deficit: on pineal calcification and melatonin excretion, Neuropsychopharmacology 21 (1999) 765–772.
[113] V. Lacoste, L. Wetterberg, Individual variations of rhythms in morning and evening types with special emphasis on seasonal differences, in: L. Wetterberg (Ed.), Light and Biological Rhythms in Man, Pergamon Press, New York, 1993, pp. 287–304.
[114] E.A. Lane, H.B. Moss, Pharmacokinetics of melatonin in man: first pass hepatic metabolism, J. Clin. Endocrinol. Metab. 61 (1985) 1214–1216.
[115] P.J. Larsen, M. Møller, J.D. Mikkelsen, Efferent projections from the periventricular and medial parvicellular subnuclei of the hypothalamic paraventricular nucleus to circumventricular organs of the rat: a *Phaseolus vulgaris*-leucoagglutinin (PHA-L) tracing study, J. Comp. Neurol. 306 (1991) 462–479.
[116] G.A. Laughlin, A.B. Loucks, S.S.C. Yen, Marked augmentation of nocturnal melatonin secretion in amenorrheic athletes, but not in cycling athletes: unaltered by opioidergic or dopaminergic blockade, J. Clin. Endocrinol. Metab. 73 (1991) 1321–1326.
[117] P. Lavie, Melatonin: role in gating nocturnal rise in sleep propensity, J. Biol. Rhythms 12 (1997) 657–665.
[118] H. Legait, E. Legait, Contribution a l'étude de la glande pinéale humaine. Étude faite a l'aide de 747 glandes, Bull. Assoc. Anat. (Nancy) 61 (1974) 107–121.
[119] E.D. Lehmann, O.C. Cockerell, P. Rudge, Somnolence associated with melatonin deficiency after pinealectomy, Lancet 347 (1996) 323.
[120] A.B. Lerner, J.D. Case, R.V. Heinzelmann, Structure of melatonin, J. Am. Chem. Soc. 81 (1959) 6084–6085.
[121] A.B. Lerner, J.D. Case, Y. Takahashi, T.H. Lee, N. Mori, Isolation of melatonin, pineal factor that lightens melanocytes, J. Am. Chem. Soc. 80 (1958) 2587.
[122] P. Levallois, M. Dumont, Y. Touitou, S. Gingras, B. Masse, D. Gauvin, E. Kroger, M. Bourdages, P. Douville, Effects of electric and magnetic fields from high-power lines on female urinary excretion of 6-sulfatoxymelatonin, Am. J. Epidemiol. 154 (2001) 601–609.
[123] A.J. Lewis, N.A. Kerenyi, G. Feuer, Neuropharmacology of pineal secretions, Drug Metab. Interact. 8 (1990) 247–312.
[124] A.J. Lewy, S. Ahmed, J.M. Latham Jackson, R.L. Sack, Melatonin shifts human circadian rhythms according to a phase–response curve, Chronobiol. Int. 9 (1992) 380–392.
[125] A.J. Lewy, V.K. Bauer, B.P. Hasler, A.R. Kendall, M.L.N. Pires, R.L. Sack, Capturing the circadian rhythms of free-running blind people with 0.5 mg melatonin, Brain Res. 918 (2001) 96–100.
[126] A.J. Lewy, B.P. Hasler, J.S. Emens, R.L. Sack, Pretreatment circadian period in free-running blind people may predict the phase angle of entrainment to melatonin, Neurosci. Lett. 313 (2001) 158–160.
[127] A.J. Lewy, R.L. Sack, C.M. Singer, D.M. White, The phase-shift hypothesis for bright light's therapeutic mechanism of action: theoretical considerations and experimental evidence, Psychopharmacol. Bull. 23 (1987) 349–353.
[128] A.J. Lewy, T.A. Wehr, F.K. Goodwin, D.A. Newsome, S.P. Markey, Light suppresses melatonin secretion in humans, Science 210 (1980) 1267–1269.
[129] P. Lissoni, S. Viviani, E. Bajetta, R. Buzzoni, A. Barreca, R. Mauri, M. Resentini, F. Morabito, D. Esposti, G. Esposti, A clinical study of the pineal gland activity in oncologic patients, Cancer 57 (1986) 837–842.
[130] R.Y. Liu, J.N. Zhou, J. van Heerikhuize, M.A. Hofman, D.F. Swaab, Decreased melatonin levels in postmortem cerebrospinal fluid in relation to aging, Alzheimer's disease, and apolipoproteinE-epsilon4/4 genotype, J. Clin. Endocrinol. Metab. 84 (1999) 323–327.
[131] M.A. Lopez-Gonzalez, J.R. Calvo, C. Osuma, J.M. Guerrero, Interaction of melatonin with human lymphocytes: evidence for binding sites coupled to potentiation of cyclic AMP stimulated by vasoactive intestinal peptide and activation of cyclic GMP, J. Pineal Res. 12 (1992) 97–104.
[132] P.R. Lowestein, C. González Solveyra, D.P. Cardinali, In vitro uptake of benzodiazepoines by rat pineal gland, J. Pineal Res. 1 (1984) 207–213.
[133] R. Luboshitzki, P. Lavie, Melatonin and sex hormone interrelationship—a review, J. Pediatr. Endocrinol. Metab. 12 (1999) 355–362.
[134] R. Luboshitzki, Z. Shen-Orr, T. Shochot, P. Herer, P. Lavie, Melatonin administered in the late afternoon decreases next day pulsatile luteinizing hormone secretion in normal men: lack of antagonism by flumazenil, Program of the 4th European Congress of Endocrinology, Seville Spain, 1998, p. 330.
[135] R. Luboshitzki, Z. Shen-Orr, O. Tzischichinsky, M. Maldonado, P. Herer, P. Lavie, Actigraphic sleep–wake patterns and urinary 6-sulfatoxymelatonin excretion in patients with Alzheimer's disease, Chronobiol. Int. 18 (2001) 513–524.
[136] A. Lukaszyk, R.J. Reiter, Histophysiological evidence for the secretion of polypeptides by the pineal gland, Am. J. Anat. 143 (1975) 451–464.
[137] K. Lushington, D. Dawson, N. Encel, L. Lack, Urinary 6-sulfatoxymelatonin cycle-to-cycle variability, Chronobiol. Int. 13 (1996) 411–421.
[138] K. Lushington, D. Dawson, D.J. Kennaway, L. Lack, The relationship between 6-sulphatoxymelatonin and polysomnographic sleep in good sleeping controls and wake maintenance insomniacs, aged 55–80 years, J. Sleep Res. 8 (1999) 57–64.
[139] K. Lushington, L. Lack, D.J. Kennaway, N. Rogers, C. van den Heuvel, D. Dawson, 6-Sulfatoxymelatonin excretion and self-reported sleep in good sleeping controls and 55–80-year-old insomniacs, J. Sleep Res. 7 (1998) 75–83.
[140] M.M. Macchi, J.N. Bruce, Z. Boulos, J.S. Terman, M. Terman, Sleep, chronotype and seasonality after pineal resection in humans, Program of the 8th Meeting of the Society for Research in Biological Rhythms, Jacksonville, FL, 2002, p. 157.
[141] G.J.M. Maestroni, The immunoendocrine role of melatonin, J. Pineal Res. 14 (1993) 1–10.
[142] G.J.M. Maestroni, MLT and the immmune-hematopeietic system, in: J. Olcese (Ed.), Melatonin after Four Decades, Kluwer Academic/Plenum Press, New York, 2000, pp. 395–405.

[143] C.D. Mahle, G.D. Goggins, P. Agarwal, E. Ryan, A.J. Watson, Melatonin modulates vascular smooth muscle tone, J. Biol. Rhythms 12 (1997) 690–696.
[144] C. Mallo, R. Zaidan, G. Galy, E. Vermeulen, J. Brun, G. Chazot, B. Claustrat, Pharmacokinetics of melatonin in man after intravenous infusion and bolus injection, Eur. J. Clin. Pharmacol. 38 (1990) 297–301.
[145] X.D. Martin, H.Z. Malina, M.C. Brennan, P.H. Hendrikson, P.R. Lichter, The ciliary body-the third organ found to synthesize idoleamines in humans, Eur. J. Ophthalmol. 2 (1992) 67–72.
[146] E.S. Maywood, E.L. Bittman, F.J. Ebling, P. Barrett, P. Morgan, M.H. Hastings, Regional distribution of iodomelatonin binding sites within the suprachiasmatic nucleus of the Syrian hamster and the Siberian hamster, J. Neuroendocrinol. 7 (1995) 215–223.
[147] C.P. McCord, F.P. Allen, Evidences associating pineal gland functions with alterations in pigmentation, J. Exp. Zool. 23 (1917) 207–224.
[148] I.M. McIntyre, T.R. Norman, G.D. Burrows, Human melatonin suppression by light is intensity dependent, J. Pineal Res. 6 (1989) 151–156.
[149] I.M. McIntyre, T.R. Norman, G.D. Burrows, S.M. Armstrong, Alterations to plasma melatonin and cortisol after evening alprazolam administration in humans, Chronobiol. Int. 10 (1993) 205–213.
[150] J.H. Meijer, W.J. Rietveld, The neurophysiology of the suprachiasmatic circadian pacemaker in rodents, Physiol. Rev. 69 (1989) 671–702.
[151] P.P.A. Mersch, Prevalence from population surveys, in: T. Partonen, A. Magnosson (Eds.), Seasonal Affective Disorder: Practice and Research, University Press Oxford, Oxford, 2001, pp. 121–140.
[152] J.D. Mikkelsen, F. Hauser, J. Olcese, Neuropeptide Y (NPY) and NPY receptors in the rat pineal gland, in: J. Olcese (Ed.), Melatonin after Four Decades, Kluwer Academic/Plenum Press, New York, 2000, pp. 95–107.
[153] J.D. Mikkelsen, M. Møller, Vasoactive intestinal peptide in the hypothalamohypophysial system of the mongolian gerbil, J. Comp. Neurol. 273 (1988) 87–98.
[154] A. Miles, S. Tidmarsh, D. Philbrick, D.M. Shaw, Diagnostic potential of melatonin analysis in pineal tumors, N. Engl. J. Med. 313 (1985) 329–330.
[155] L.E. Miles, W.C. Dement, Sleep and aging, Sleep 3 (1980) 119–120.
[156] K. Mishima, T. Tozawa, K. Satoh, Y. Matsumoto, Y. Hishikawa, M. Okawa, Melatonin secretion rhythm in patients with senile dementia of Alzheimer's type with disturbed sleep–waking, Biol. Psychiatry 45 (1999) 417–421.
[157] M. Møller, Presence of a pineal nerve (nervus pinealis) in the human fetus: light and electron microscopical study of the innervation of the pineal gland, Brain Res. 154 (1978) 1–12.
[158] M. Møller, The structure of the pinealopetal innervation of the mammalian pineal gland, Microsc. Res. Tech. 21 (1992) 188–204.
[159] K. Møllgard, M. Møller, On the innervation of the human fetal pineal gland, Brain Res. 52 (1973) 428–432.
[160] P. Monteleone, M. Maj, M. Fusco, C. Orazzo, D. Kemali, Physical exercise at night blunts the nocturnal increase of plasma melatonin levels in healthy humans, Life Sci. 47 (1990) 1989–1995.
[161] P. Monteleone, M. Natale, A. La Rocca, M. Maj, Decreased nocturnal secretion of melatonin in drug-free schizophrenics: no change after subchronic treatment with antipsychotics, Neuropsychobiology 36 (1997) 159–163.
[162] R.Y. Moore, Neural control of the pineal gland, Behav. Brain Res. 73 (1996) 125–130.
[163] R.Y. Moore, P. Sibony, Enkephalin-like immunoreactivity in neurons of the human pineal gland, Brain Res. 457 (1988) 395–398.
[164] Y. Moriyama, H. Yamada, M. Hayashi, S. Yatsushiro, Intrinsic glutaminergic system negatively regulates melatonin synthesis in mammalian pineal gland, in: J. Olcese (Ed.), Melatonin after Four Decades, Kluwer Academic/Plenum Press, New York, 2000, pp. 83–90.
[165] M. Morris, L. Lack, J. Barrett, The effect of sleep/wake state on nocturnal melatonin excretion, J. Pineal Res. 9 (1990) 133–138.
[166] J. Murata, Y. Sawamura, J. Ikeda, S. Hashimoto, K. Honma, Twenty-four hour rhythm of melatonin in patients with a history of pineal and/or hypothalamo-neurohypophyseal germinoma, J. Pineal Res. 25 (1998) 159–166.
[167] B.L. Myers, P. Badia, Changes in circadian rhythms and sleep quality with aging: mechanisms and interventions, Neurosci. Biobehav. Rev. 19 (1995) 553–571.
[168] R. Nave, P. Herer, I. Haimov, A. Shlitner, P. Lavie, Hypnotic and hypothermic effects of melatonin on daytime sleep in humans: lack of antagonism by flumazenil, Neurosci. Lett. 214 (1996) 123–126.
[169] R.J. Nelson, D.L. Drazen, Melatonin mediates seasonal adjustments in immune function, Reprod. Nutr. Dev. 39 (1999) 383–398.
[170] B. Neri, C. Fiorelli, F. Moroni, G. Nicita, M.C. Paoletti, R. Ponchietti, A. Raugei, G. Santoni, A. Tripitelli, G. Grechi, Modulation of human lymphoblastoid interferon activity by melatonin in metastatic renal cell carcinoma. A phase II study, Cancer 73 (1994) 3015–3019.
[171] E.A. Neuwelt, A.J. Lewy, Disappearance of plasma melatonin after removal of a neoplastic pineal gland, N. Engl. J. Med. 308 (1983) 1132–1135.
[172] Y. Ohashi, N. Okamoto, K. Uchida, M. Iyo, N. Mori, Y. Morita, Daily rhythm of serum melatonin levels and effect of light exposure in patients with dementia of the Alzheimer's type, Biol. Psychiatry 45 (1999) 1646–1652.
[173] Y. Okatani, Y. Sagara, Amplification of nocturnal melatonin secretion in women with functional secondary amnorrhea: relation to endogenous oestrogen concentrations, Clin. Endocrinol. 41 (1994) 763–770.
[174] S.F. Pang, Y. Li, D.H. Jiang, B. Chang, B.L. Xie, Acute cerebral hemorrhage changes the nocturnal surge of plasma melatonin in humans, J. Pineal Res. 9 (1990) 193–208.
[175] M.A. Pappolla, Y.J. Chyan, B. Poeggeler, B. Frangione, G. Wilson, J. Ghiso, R.J. Reiter, An assessment of the antioxidant and antiamyloidogenic properties of melatonin: implications for Alzheimer's disease, J. Neural Trans. 107 (2000) 203–231.
[176] T. Partonen, Extrapineal melatonin and exogenous serotonin in seasonal affective disorder, Med. Hypotheses 51 (1998) 441–442.
[177] P.D. Penev, P.C. Zee, Melatonin: a clinical perspective, Ann. Neurol. 42 (1997) 545–553.
[178] P. Pévet, Physiological role of neuropeptides in the mammalian pineal gland, in: A. Foldes, R.J. Reiter (Eds.), Advances in Pineal Research, vol. 6, Libbey & Co, London, 1991, pp. 275–282.
[179] P. Phansuwan-Pujito, J.D. Mikkelsen, P. Govitrapong, M. Møller, A cholinergic innervation of the bovine pineal gland visualized by immunohistochemical detection of choline acetyltransferase-immunoreactive nerve fibers, Brain Res. 545 (1991) 49–58.
[180] M.L.N. Pires, A.A. Benedito-Silva, L. Pinto, L. Souza, L. Vismari, H.M. Calil, Acute effects of low doses of melatonin on the sleep of young healthy subjects, J. Pineal Res. 31 (2001) 326–332.
[181] M.F. Poirier, Current trends in clinical psychiatric research, Presse Med. 19 (1998) 2185–2189.
[182] A.M.S. Poon, S.F. Pang, Pineal melatonin-immune system interaction, in: P.L. Tang, S.F. Pang, R,J. Reiter (Eds.), Melatonin: A Universal Photoperiodic Signal with Diverse Action, Front Horm Res., vol. 21, Karger, Basel, 1996, pp. 71–83.
[183] A.M.S. Poon, A.S.Y. Mak, H.T. Luk, Melatonin and 2[125]iodomelatonin binding sites in the human colon, Endocrinol. Res. 22 (1996) 77–94.

[184] I. Provencio, I.R. Rodriguez, G. Jiang, W.P. Hayes, E.F. Moreira, M.D. Rollag, A novel human opsin in the inner retina, J. Neurosci. 20 (2000) 600–605.
[185] W.B. Quay, Circadian rhythm in rat pineal serotonin and its modification of estrous cycle and photoperiod, Gen. Comp. Endocrinol. 3 (1963) 1473–1479.
[186] W.B. Quay, Circadian and estrous rhythms in pineal melatonin and 5-hydroindole-3-indole acetic acid, Proc. Soc. Exp. Biol. Med. 115 (1964) 710–714.
[187] K. Reid, C. Van den Heuvel, D. Dawson, Day-time melatonin administration: effects on core temperature and sleep onset latency, J. Sleep Res. 5 (1996) 150–154.
[188] R.J. Reiter, The mammalian pineal gland: structure and function, Am. J. Anat. 162 (1981) 287–313.
[189] R.J. Reiter, Pineal melatonin: cell biology of its synthesis and of its physiological interactions, Endocr. Rev. 12 (1991) 151–180.
[190] R.J. Reiter, Cytoprotective properties of melatonin: presumed association with oxidative damage and aging, Nutrition 14 (1998) 691–696.
[191] R.J. Reiter, M.I. Pablos, T.T. Agapito, J.M. Guerrero, Melatonin in the context of the free radical theory of aging, Ann. N. Y. Acad. Sci. 786 (1986) 362–378.
[192] R.J. Reiter, D. Melchiorri, E. Sewerynek, B. Poeggeler, L. Barlow-Walden, J. Chuang, C.G. Ortiz, D. Acuna Castroviejo, A review of the evidence supporting melatonin's role as an antioxidant, J. Pineal Res. 18 (1995) 1–11.
[193] S.M. Reppert, C. Godson, C.D. Mahle, D.R. Weaver, S. Slaugenhaupt, J.F. Gusella, Molecular characterization of a second melatonin receptor expressed in human retina and brain: the Mel1b melatonin receptor, Proc. Natl. Acad. Sci. USA 92 (1995) 8734–8738.
[194] S.M. Reppert, D.R. Weaver, T. Ebisawa, C.D. Mahle, L.F. Kolakowski, Cloning of a melatonin-related receptor from human pituitary, FEBS Lett. 386 (1996) 219–224.
[195] S.M. Reppert, D.R. Weaver, S.A. Rivkees, E.G. Stopa, Putative melatonin receptors in a human biological clock, Science 242 (1988) 78–81.
[196] W.A. Robinson, Melatonin in the treatment of the human malignant metastatic melanoma, in: Proceedings of the NATO workshop The Pineal Gland and Its Hormones: Fundamentals and Clinical Perspectives, Erice, Italy, 1994.
[197] O.K. Ronnekleiv, Distribution in the macaque pineal of nerve fibers containing immunoreactive substance P, vasopressin, oxytocin, and neurophysins, J. Pineal Res. 5 (1998) 259–271.
[198] N.E. Rosenthal, D.A. Sack, J.C. Gillin, A.J. Lewy, Y. Davenport, P.S. Mueller, D.A. Newsome, T.A. Wehr, Seasonal affective disorder: a description of the syndrome and preliminary findings with light therapy, Arch. Gen. Psychiatry 41 (1984) 72–80.
[199] R.L. Sack, R.W. Brandes, A.R. Kendall, A.J. Lewy, Entrainment of free-running circadian rhythms by melatonin in blind people, N. Engl. J. Med. 343 (2000) 1070–1077.
[200] A. Sakotnik, P.M. Liebmann, K. Stoschitzky, P. Lercher, K. Schauenstein, W. Klein, B. Eber, Decreased melatonin synthesis in patients with coronary artery disease, Eur. Heart J. 20 (1999) 1314–1317.
[201] C.A. Sasek, R.E. Zigmond, Localization of vasoactive intestinal peptide- and peptide histidine isoleucine amide-like immunoreactivities in the rat superior cervical ganglion and its nerve trunks, J. Comp. Neurol. 280 (1989) 522–532.
[202] J. Scher, E. Wankiewicz, G.M. Brown, H. Fujieda, Melatonin receptor in the human retina: expression and localization, Invest Ophthalmol. Vis. Sci. 43 (2002) 889–897.
[203] B. Selmaoui, J. Lambrozo, Y. Touitou, Magnetic fields and pineal function in humans: evaluation of nocturnal acute exposure to extremely low frequency magnetic fields on serum melatonin and urinary 6-sulfatoxymelatonin circadian rhythms, Life Sci. 58 (1996) 1539–1549.
[204] Y. Shiotani, M. Yamano, S. Shiosaka, P.C. Emson, C.J. Hillyard, S. Girgis, I. MacIntyre, Distribution and origins of substance P (SP)-, calcitonin gene-related peptide (CGRP)-, vasoactive intestinal polypeptide (VIP)- and neuropeptide Y (NPY)-containing nerve fibers in the pineal gland of gerbils, Neurosci. Lett. 70 (1986) 187–192.
[205] T. Shochat, I. Haimov, P. Lavie, Melatonin—the key to the gate of sleep, Ann. Med. 30 (1998) 109–114.
[206] V. Simonneaux, A. Ouichou, C. Craft, P. Pévet, Presynaptic and postsynaptic effect of neuropeptide Y in the rat pineal gland, J. Neurochem. 62 (1994) 2464–2471.
[207] V. Simonneaux, C. Ribelayga, J.M. Miguez, P. Pévet, Physiological role of neuropeptides in the mammalian pineal gland, in: P.L. Tang, S.F. Pang, R.J. Reiter (Eds.), Melatonin: A Universal Photoperiodic Signal with Diverse Actions, Front Horm Res., vol. 21, Karger, Basel, 1996, pp. 24–29.
[208] Z. Skribanek, L. Balaspiri, M. Mak, Interaction between synthetic amyloid-beta-peptide (1–40) and its aggregation inhibitors studied by electrospray ionization mass spectrometry, J. Mass Spectrom. 36 (2001) 1226–1229.
[209] A. Smolen, Morphology of synapses in the autonomic nervous system, J. Electron Microsc. Tech. 10 (1988) 187–204.
[210] D.L. Sparks, Anatomy of a new paired tract of the pineal gland in humans, Neurosci. Lett. 248 (1998) 179–182.
[211] J.H. Stehle, N.S. Foulkes, C.A. Molina, V. Simonneaux, P. Pévet, P. Sassone-Corsi, Adrenergic signals direct rhythmic expression of transcriptional repressor CREM in the pineal gland, Nature 365 (1993) 314–320.
[212] D. Steinhilber, M. Brungs, O. Werz, I. Wiesenberg, C. Danielsson, J.P. Kahlen, S. Nayeri, M. Schrader, C. Carlberg, The nuclear receptor for melatonin represses 5-lipoxygenase gene expression in human B lymphocytes, J. Biol. Chem. 270 (1995) 7037–7040.
[213] B.M. Stone, C. Turner, S.L. Mills, A.N. Nicholson, Hypnotic activity of melatonin, Sleep 23 (2000) 663–669.
[214] R.J. Strassman, C.R. Qualls, E.J. Lisansky, G.T. Peake, Elevated rectal temperature produced by all-night bright light is reversed by melatonin infusion in men, J. Appl. Physiol. 71 (1991) 2178–2182.
[215] F.K. Studnicka, Zur Kenntnis der Parietalorgane under der sog, Parphyse der niederen Wirbeltiere, Verh. Anat. Ges. Jena 14 (1900) 101–110.
[216] D. Sugden, D.C. Klein, A cholera toxin substrate regulates cyclic GMP content of rat pinealocytes, J. Biol. Chem. 262 (1987) 7447–7450.
[217] J.S. Takahashi, ICER is nicer at night (sir!), Curr. Biol. 4 (1994) 165–168.
[218] N. Tamaki, K. Shirataki, T. Lin, M. Masumura, S. Katayama, S. Matsumoto, Cysts of the pineal gland, Child Nerv. Syst. 5 (1989) 172.
[219] L. Tamarkin, D. Danforth, A. Lichter, Decreased nocturnal plasma melatonin peak in patients with estrogen positive breast cancer, Science 216 (1982) 1003–1005.
[220] D.-Z. Tan, B. Poeggeler, R.J. Reiter, L.-D. Chen, S. Chen, L.C. Manchester, L.R. Barlow-Walson, The pineal hormone melatonin inhibits DAN-adduct formation induced by chemical carcinogen safrole in vitro, Cancer Lett. 70 (1993) 65–71.
[221] D.-Z. Tan, B. Poeggeler, R.J. Reiter, L.-D. Chen, S. Chen, L.C. Manchester, L.R. Barlow-Walson, Both physiological and pharmacological levels of melatonin reduce DNA adduct formation induced by carcinogen safrole, Carcinogenesis 15 (1994) 215–218.
[222] J.S. Terman, M. Terman, E.-S. Lo, T.B. Cooper, Circadian time of morning light administration and therapeutic response in winter depression, Arch. Gen. Psychiatry 58 (2001) 69–75.
[223] K. Thapan, J. Arendt, D.J. Skene, An action spectrum for melatonin suppression: evidence for a novel non-rod, non-cone photoreceptor system in humans, J. Physiol. 535 (1) (2001) 261–267.

[224] L. Thomas, J.E. Drew, D.R. Abramovich, L.M. Williams, The role of melatonin in the human fetus (review), Int. J. Mol. Med. 1 (1998) 539–543.
[225] M.I. Vacas, M.M. Del Zar, M. Martinuzzo, D.P. Cardinali, Binding sites for [^{3}H]-melatonin in human platelets, J. Pineal Res. 13 (1992) 60–65.
[226] C.J. van den Heuvel, K.J. Reid, D. Dawson, Effect of atenolol on nocturnal sleep and temperature in young men: reversal by pharmacological doses of melatonin, Physiol. Behav. 61 (1997) 795–802.
[227] H.P.A. Van Dongen, G. Maislin, G.A. Kerkhof, Repeated assessment of the 24-h profile of blood pressure under constant routine, Chronobiol. Int. 18 (2001) 85–98.
[228] R.J. van Vuuren, M.J. Pitout, C.H. van Aswegen, J.J. Theron, Putative melatonin receptor in human spermatozoa, Clin. Biochem. 25 (1992) 125–127.
[229] G.M. Vaughan, Melatonin in humans, Pineal Res. Rev. 2 (1984) 141–201.
[230] D.P. Veerman, B.P. Imholz, W. Wieling, K.H. Wesseling, G.A. van Montfrans, Circadian profile of sytemic hemodynamics, Hypertension 26 (1995) 55–59.
[231] M. Viljoen, M.E. Steyn, B.W. Van Rensburg, S.G. Reinach, Melatonin in chronic renal failure, Nephron 60 (1992) 138–143.
[232] L. Vollrath, The Pineal Organ, Springer, Berlin, 1981.
[233] L. Vollrath, Functional anatomy of the human pineal gland, in: R.J. Reiter (Ed.), The Pineal Gland, Raven Press, New York, 1984, pp. 285–322.
[234] K. von Treuer, T.R. Norman, S.M. Armstrong, Overnight plasma melatonin, cortisol, prolactin, TSH, under conditions of normal sleep, sleep deprivation, and sleep recovery, J. Pineal Res. 20 (1996) 7–14.
[235] D. Vondrasova, I. Hájek, H. Illnerová, Exposure to long summer days affects the human melatonin and cortisol rhythms, Brain Res. 759 (1997) 166–170.
[236] D. Vondrasová-Jel•´nková, I. Hájek, H. Illnerová, Adjustment of the human melatonin and cortisol rhythms to shortening of the natural summer photoperiod, Brain Res. 816 (1999) 249–253.
[237] B.C.G. Voordouw, R. Euser, R.E.R. Verdonk, B.T.H. Alberda, F.H. De Jong, A.C. Drogenduk, B.C.J.M. Fauser, M. Cohen, Melatonin and melatonin-progestin combinations alter pituitary-ovarian function in women and can inhibit ovulation, J. Clin. Endocrinol. Metab. 74 (1992) 108–117.
[238] P. Vorkapic, F. Waldhauser, R. Bruckner, C. Biegelmayer, M. Schmidbauer, G. Pendl, Serum melatonin levels: a new neurodiagnostic tool in pineal region tumors, Neurosurgery 21 (1987) 817–824.
[239] F. Waldhauser, P.A. Boepple, M. Schemper, M.J. Mansfield, W.F. Crowley Jr., Serum melatonin in central precocious puberty is lower than in age-matched prepubertal children, J. Clin. Endocrinol. Metab. 73 (1981) 793–796.
[240] F. Waldhauser, B. Ehrhart, E. Forster, Clinical aspects of the melatonin action: impact on development, aging and puberty, involvement of melatonin in psychiatric disease and importance of neuroimmunoendocrine interactions, Experientia 49 (1993) 671–681.
[241] F. Waldhauser, H. Frisch, M. Waldhauser, G. Weiszenbacher, U. Zeitlhuber, R.J. Wurtman, Fall in nocturnal serum melatonin during prepuberty and pubescence, Lancet 1 (1985) 362–365.
[242] D.R. Weaver, S.M. Reppert, The Mel_{1a} melatonin receptor gene is expressed in human suprachiasmatic nucleus, Neuro Rep. 8 (1996) 109–112.
[243] S.M. Webb, M. Puig-Domingo, Role of melatonin in health and disease, Clin. Endocrinol. 42 (1995) 221–234.
[244] T.A. Wehr, The durations of human melatonin secretion and sleep respond to changes in daylength (photoperiod), J. Clin. Endocrinol. Metab. 73 (1991) 1276–1280.
[245] T.A. Wehr, W.C. Duncan Jr., L. Sher, D. Aeschbach, P.J. Schwartz, E.H. Turner, T.T. Postolache, N.E. Rosenthal, A circadian signal of change of season in patients with Seasonal Affective Disorder, Arch. Gen. Psychiatry 58 (2001) 1108–1114.
[246] T.A. Wehr, D.A. Sack, F. Jacobsen, L. Tamarkin, J. Arendt, N.E. Rosenthal, Phototherapy of seasonal affective disorder: time of day and suppression of melatonin are not critical for antidepressant effect, Arch. Gen. Psychiatry 43 (1986) 870–875.
[247] E. Weihe, J.H. Tao-Cheng, M.K.H. Schäfer, J.D. Erickson, L.E. Eiden, Visualization of the vesicular acetylcholine transporter in cholinergic nerve terminals and its targeting to specific populations of small synaptic vesicles, Proc. Natl. Acad. Sci. USA 93 (1996) 3547–3552.
[248] L. Wetterberg, Melatonin and affective disorders, Ciba Found Symp. 117 (1985) 235–265.
[249] J. Wikner, U. Hirsch, L. Wetterberg, S. Rodjmark, Fibromyalgia—a syndrome associated with decreased nocturnal melatonin secretion, Clin. Endocrinol. 49 (1998) 179–183.
[250] B.W. Wilson, H.J. Lynch, Y. Ozaki, 5-Methoxytryptophol in rat serum and pineal: detection, quantitation, and evidence for daily rhythmicity, Life Sci. 23 (1978) 1019–1023.
[251] A. Wirz-Justice, P. Graw, K. Krauchi, B. Gisin, A. Jochum, J. Arendt, H.U. Fisch, C. Buddeberg, W. Poldinger, Light therapy in seasonal affective disorder is independent of time of day or circadian phase, Arch. Gen. Psychiatry 50 (1993) 929–937.
[252] R.J. Wurtman, H.J. Lynch, W.Q. Sturner, Melatonin in humans: possible involvement in SIDS, and use in contraceptives, in: J. Arendt, P. Pévet (Eds.), Advances in Pineal Research, vol. 5, John Libbey, London, 1991, pp. 319–327.
[253] R.J. Wurtman, C.M. Rose, C. Chou, F.F. Larin, Daily rhythms in the concentrations of various amino acids in human plasma, N. Engl. J. Med. 279 (1968) 171–175.
[254] H. Yamada, A. Ogura, A. Yamaguchi, Y. Moriyama, Acetylcholine triggers L-glutamate exocytosis via nicotinic receptors and inhibits melatonin synthesis in rat pinealocytes, J. Neurosci. 18 (1998) 4946–4952.
[255] N. Yamada, H. Iwasa, S. Mori, N. Kurokawa, K. Fujimoto, K. Kawashima, T. Masuzawa, Melatonin secretion in normal pressure hydrocephalus after cerebral aneurysm rupture—investigation before and after ventriculoperitoneal shunt, Neurologia Medico-Chirurgica 31 (1991) 490–497.
[256] S.-M. Yie, L.P. Niles, E.V. Youglai, Melatonin receptors on human granulosa cell membranes, J. Clin. Endocrinol. Metab. 80 (1995) 1747–1749.
[257] S.D. Youngstedt, D.F. Kripke, J.A. Elliott, Melatonin excretion is not related to sleep in the elderly, J. Pineal Res. 24 (1998) 142–145.
[258] J.M. Zeitzer, J.E. Daniels, J.F. Duffy, E.B. Klerman, T.L. Shanahan, D.-J. Dijk, C.A. Czeisler, Do plasma melatonin concentrations decline with age, Am. J. Med. 107 (1999) 432–436.
[259] I.V. Zhdanova, R.J. Wurtman, H.J. Lynch, J.R. Ives, A.B. Dollins, C. Morabito, J.K. Matheson, D.L. Schomer, Sleep-inducing effects of low doses of melatonin ingested in the evening, Clin. Pharmacol. Ther. 57 (1995) 552–558.
[260] I.V. Zhdanova, R.J. Wurtman, C. Morabito, V.R. Piotrovska, H.J. Lynch, Effects of low oral doses of melatonin, given 2–4 h before habitual bedtime, on sleep in normal young humans, Sleep 19 (1996) 423–431.
[261] I.V. Zhdanova, R.J. Wurtman, M.M. Regan, J.A. Taylor, J.P. Shi, O.U. Leclair, Melatonin treatment for age-related insomnia, J. Clin. Endocrinol. Metab. 86 (2001) 4727–4747.
[262] N. Zisapel, H. Matzkin, E. Gilad, Melatonin receptors in human prostate epithelial cells, in: Y. Touitou (Ed.), Biological Clocks, Mechanisms and Applications, Elsevier, Amsterdam, 1998, pp. 295–299.
[263] C. Zrenner, Theories of pineal function from classical antiquity to 1900: a history, in: R.J. Reiter (Ed.), Pineal Research Reviews III, Alan R. Liss, New York, 1985, pp. 1–40.