13.11 The pineal gland and melatonin 2553

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ESSENTIALS The pineal gland transduces light–dark cycles for the timing of body rhythms by secretion of melatonin, an endogenous indoleamine de- rived from tryptophan, the concentrations of which in plasma and cerebrospinal fluid are up to 100 times higher at night than in the daytime. This exerts its effects through transmembrane, G-protein coupled receptors (MT1 and MT2), and nuclear receptors primarily in the suprachiasmatic nucleus, pars tuberalis of the pituitary gland and hypothalamus. The natural period of the human circadian system is on average 24.1 to 24.3 h, and the principal resetting agent is light. Exogenous melatonin can shift the timing of the internal clock to earlier and later times, and synchronize a free-running clock that is not properly entrained to the 24-h day, hence it may have a therapeutic role for disorders of sleep rhythm including jet lag, in shift workers, and in blind people. It has proved useful for sleep disorders in neurologic- ally disabled children. Exogenous melatonin also has rapid transitory ‘soporific’ or sleep-inducing effects and may be used to hasten sleep onset in suitable circumstances. A combination of sleep induction and circadian realignment is most effective. Numerous reports of antioxidant/free-radical scavenging/neuroprotective/anticancer ef- fects (in large doses) have yet to find a confirmed clinical application. Introduction The mammalian pineal gland is a secretory organ. Whereas in fish and amphibians it is directly photoreceptive, in reptiles and birds it has a mixed photoreceptor and secretory function. Although an endocrine function was considered for many years, this was only given credibility in 1958 by the pioneering work of Lerner, who iso- lated a small molecule from bovine pineal glands that he named melatonin because it caused blanching of melanophores in am- phibian skin. The primary function of the pineal gland in all species studied to date is to transduce information concerning light–dark cycles to body physiology, particularly for the organization of body rhythms, via the secretion of its major hormone melatonin. In some birds and lower vertebrates, it serves as a rhythm generating system, or biological clock. In mammals, it is concerned with the coordin- ation of rhythm physiology without having the capacity to act as a rhythm generator. In humans, the gland has been known since an- tiquity. Many questions remain unanswered about the function of the human pineal gland, but its secretion of the chronobiotic mol- ecule melatonin has prompted enormous interest in the fields of travel medicine, neurophysiology, and endocrine research. The pineal gland Structure The pineal gland is less than

1 cm in its longest diameter and weighs less than 0.2 g; it lies above the posterior aspect of the third cerebral ven- tricle. The major cellular component of the normal mammalian pineal gland, the pinealocyte, is believed to have evolved from truly photo- receptive cells in lower vertebrates and structural remnants of the outer segments of photoreceptor cells are reported in higher vertebrates. It also contains neuroglial components, principally of astrocytic type, which occasionally become malignant. Human pineal tissue calcifies with age, but this does not necessarily diminish its secretory activity. The pineal gland is considered to reside outside the func- tional blood–brain barrier. Pathology Tumours of the pineal region in children are frequently associated with abnormal pubertal development. Much evidence suggests that preco- cious puberty in such cases is due to the production of human chori- onic gonadotrophin (β-hCG) by germ cell tumours of the pineal gland. Delayed puberty has also been associated with pineal tumours. Pineal tumours are heterogeneous and may arise from germ cells (teratomas, germinomas, choriocarcinomas, endodermal sinus tumours, mixed germ cell tumours), pineal parenchymal cells (pineoblastoma and pineocytoma), and the supporting stroma (gliomas). Classification of pineal parenchymal tumours is complicated by the presence of mixed pineocytoma-pineoblastoma types, some with intermediate differ- entiation. A new classification has been proposed recently, based on histological features, which is closely related to patient survival. Treatment of pineal tumours by surgical excision or radiation ap- pears to suppress melatonin secretion leading to sleeping difficulties; 13.11 The pineal gland and melatonin J. Arendt and Timothy M. Cox

section 13 Endocrine disorders 2554 melatonin replacement therapy has been reported to benefit such pa- tients with defective melatonin release. However not all reports are con- sistent and two recent studies showed no effect of pinealectomy on sleep assessed pre- and post-operatively in humans by polysomnography, and in rats. Melatonin is a darkness hormone not a sleep hormone. Melatonin Biosynthesis Melatonin, like serotonin, is an endogenous indoleamine derived from tryptophan. The first step in indoleamine synthesis is the 5- hydroxylation of tryptophan by tryptophan hydroxylase—an en- zyme with requirements for dioxygen, iron, and tetrahydrobiopterin. 5-Hydroxytryptophan (5HTP) is then decarboxylated to serotonin or 5-hydroxytryptamine (5HT). The enzyme arylalkylamine N- acetyltransferase (AANAT), regulated by the sympathetic trans- mitter noradrenaline, then acetylates 5HT to N-acetylserotonin (NAS) and this appears to be the rate-limiting step in melatonin syn- thesis. The enzyme is localized principally in the pineal gland but also in the retina, the skin, within specific cells in the upper gastrointes- tinal tract, and with minor expression in bone marrow, lymphocytes, and certain epithelia. The final step in the synthesis is carried out by hydroxyindole-O-methyl transferase (HIOMT) (Figs. 13.11.1a and 13.11.1b). This enzyme is now known as N-acetylserotonin O-methyltransferase (ASMT). Melatonin receptors Melatonin binds to specific receptors including the seven transmem- brane G-protein-coupled MT1 and MT2 receptors, as well as nuclear receptors RZR/ROR orphan receptor family and downstream tran- scription factors that are associated with melatonin signalling. A third site, named MT3, is the enzyme quinone reductase type 2, which mela- tonin and its congeners bind and inhibit with high affinity. This action is shared with the natural product resveratrol, and indicates a potential application for melatonin as an antioxidant in pleiotropic detoxifica- tion processes, including the treatment and prevention of cancer. Membrane G-protein receptors for melatonin are principally expressed in the nervous system but they have been found in nu- merous other locations. The nuclear transcription factor appears to be expressed in the periphery. There is emerging evidence that a nuclear signalling pathway with ligand-induced

control of target gene transcription, mediates some functions of melatonin. The MT2 melatonin receptors have been implicated in mediating learning and memory in experimental mice, and there is also evidence that their activation alters electrophysiological phenomena associated with memory, such as long-term potentiation in neurones; loss of these receptors also decreases hippocampal synaptic plasticity. Melatonin has been reported to control expression of the 5-lipoxygenase gene; Third ventricle PVN Pineal SCN SCG Spinal cord (a) Pituitary Eye NH2 CH2CH COOH NH2 CH2CH CH2CH2NH2 CH2CH2NHCOCH3 CH2CH2NHCOCH3 CH3O HO HO HO N H N H N H N H N H COOH TRYPTOPHAN TRYPTOPHAN-5-HYDROXYLASE 5 HTP- DECARBOXYLASE SEROTONIN-N-ACETYLTRANSFERASE NAT or AANAT HYDROXYINDOLE-0-METHYL TRANSFERASE (HIOMT) MELATONIN 5-HYDROXYTRYPTOPHAN (5HTP) 5-HYDROXYTRYPTAMINE (5HT, SEROTONIN) N-ACETYSEROTONIN (NAS) (N-ACETYL-5-METHOXYTRYPTAMINE) Fig. 13.11.1 (a) Melatonin synthesis and the principal neural pathways innervating the pineal gland. SCN, suprachiasmatic PVN, paraventricular nucleus; SCG, superior cervical ganglion. (b) Control of melatonin synthesis in the mammalian pineal gland. (a) Source data from Tamarkin K, Baird CJ, Almeida OF (1985). Melatonin: A coordinating signal for mammalian reproduction. Science, 227, 714–20. (b) Reprinted by permission from Springer Nature: Springer Cell and Tissue Research. Ganguly S, Coon SL, Klein DC (2002). Control of melatonin synthesis in the mammalian pineal gland: the critical role of serotonin acetylation. Cell Tissue Res, 309, 127–37, Copyright © 2002.

13.11 The pineal gland and melatonin 2555 the cognate enzyme is not implicated in circadian rhythms but is expressed in myeloid cells and participates in allergic and inflam- matory reactions. Melatonin (formal chemical name, N-acetyl-5-methoxytryptamine) has been found within membrane-bound bodies in pinealocytes. In experimental animals these show light-dependent morphological changes associated with melatonin secretion under altered envir- onmental light conditions. The pineal gland is the principal source of circulating melatonin in mammals, indeed pinealectomy leads to undetectable melatonin concentrations in blood. Synthesis else- where (e.g. in the retina), seems to change local concentrations only. Melatonin appears to exert its main effects through MT1 receptors in the infundibular part of the pituitary gland, through MT1 and MT2 re- ceptors in the central biological rhythm generating system of the brain (the suprachiasmatic nuclei of the hypothalamus) and other regions of the hypothalamus that modulate the secretion of pituitary hormones, and that influence core body temperature and other functions. The role of melatonin and the pineal gland in photoperiodism In all species studied to date, melatonin is normally synthesized and secreted at night. This rhythm is circadian in nature (i.e. it is en- dogenously driven by the activity of the suprachiasmatic nuclei). Exposure to light influences the secretion of melatonin, and mela- tonin release is suppressed particularly by blue light (wavelength 460–480 nm) in a manner that increases with length of exposure and intensity of luminance. The length of the day (photoperiod) strongly influences melatonin secretion: the longer the night, the longer the duration of secretion. The long-standing tendency of humans to alter their light environment since the discovery of fire renders this relationship hard to show, except under conditions in which the dur- ation of total darkness is altered. However, the seasonal physiology of many animals is regulated by the photoperiod and changing dur- ation of melatonin secretion is critical for inducing several specific seasonal responses (e.g. reproduction, coat growth). Melatonin influences production of gonadotrophins and gonadal hormones via actions within the hypothalamus. There is recent evi- dence for a molecular mechanism within the pars tuberalis of the pi- tuitary, which links the short duration, long day melatonin signal to a hypothalamic increase of triiodothyronine (T3) through a thyroid- stimulating hormone/deiodinase2 paracrine mechanism.

The local synthesis of type 2 deiodinase (Dio2) promotes triiodothyronine (T3) production and summer biology, whereas type 3 deiodinase (Dio3) promotes T3 degradation and winter biology. However, melatonin controls seasonal variations in prolactin by a direct ac- tion on the pars tuberalis of the pituitary. This structure is the major site of melatonin receptors (MT1) in most species. Photoperiod- dependent gene expression in the pars tuberalis is directly modified by melatonin (Fig. 13.11.2). Exogenous melatonin can be used as the photoperiodic signal and has been commercialized to permit regulation of the breeding season in useful domesticated species such as sheep, goats, and mink. In animals and humans there is now evidence for an alter- native photoreceptive system, which is independent of retinal rods Fig. 13.11.1 Continued

section 13 Endocrine disorders 2556 SUMMER Long days Short melatonin profile WINTER Short days Long melatonin profile (a) Cry Per CCG BMal Clk MT1 & MT2 PVN (b) SCG NA WINTER TSH DIO2 T4 T3 TSH DIO2 Prolactin LH GnRH T4 T3 WINTER SUMMER SUMMER RETINA HYPO-THALAMUS RHT-GLUTAMATE SCN MELATONIN PINEAL GLAND PARS TUBERALIS Per NAT MT1 MT2 Per Cry Fig. 13.11.2 Photoperiodic and circadian mechanisms. (a) The duration of melatonin secretion changes with daylength, providing an internal time cue for the organization of daylength-dependent seasonal functions in photoperiodic species. This changing duration can be seen in humans if they are maintained in different durations of total darkness. However, domestic intensity light at night is sufficient to greatly diminish or eliminate this photoperiodic response.
(b) Diagrammatic representation of the control of production and the functions of melatonin with regard to seasonal and circadian timing mechanisms. RHT, retino-hypothalamic tract; NA, noradrenalin; SCN, suprachiasmatic nucleus; PVN, paraventricular nucleus; SCG, superior cervical ganglion; TSH, thyroid-stimulating hormone, DIO2, type II thyroid hormone deiodinase. MT1 and MT2, melatonin receptor subtypes. The melatonin rhythm is generated by a closed-loop negative feedback of clock gene expression in the SCN. Clk and BMal, positive stimulatory elements; Per and Cry, negative elements; CCG, clock-controlled genes. Per and NAT mRNA oscillate in the pineal, although posttranscription control is evident in some species. Melatonin influences SCN activity via two or more receptors. MT2 appears to be primarily the phase-shifting receptor in rodents, whereas MT1 is associated with suppression of SCN electrical activity. The MT2 receptor was first characterized in the retina and influences dopamine release. Melatonin conveys photoperiodic information influencing the patterns of clock gene expression in the pars tuberalis for the control of seasonal prolactin variations via an MT1 receptor. (b) Adapted (with permission) from an original diagram by Elisabeth Maywood, MRC Laboratory of Molecular Biology, Neurobiology Division, Cambridge, United Kingdom. Modified from Encyclopedia of Endocrine diseases.

13.11 The pineal gland and melatonin 2557 or cones, utilizes light-sensitive retinal ganglion cells and a distinct photopigment (melanopsin). It serves to mediate the physiological (but nonvisual) effects of light (usually in concert with rods and cones). This photoreceptive apparatus responds preferentially to short-wavelength light, 460–480 nm. Melatonin and circadian rhythms Rhythmic melatonin secretion leads to concentrations in the plasma or cerebrospinal fluid that are up to 100 times greater at night than in the daytime, with very large interindividual but con- sistent intraindividual variation. These fluctuations are used to assess the timing of the human biological clock: the secretion pro- file of melatonin provides, in the periphery, the most accurate and sensitive index of the activity of the suprachiasmatic nuclei. In the diagnosis of circadian rhythm disorders, blood, and salivary deter- minations of melatonin and/or measures of the principal metabolite, 6-sulphatoxymelatonin (aMT6s) in urine are useful. Maximum con- centrations are

observed in childhood and melatonin concentra- tions decline thereafter with age. The role of endogenous melatonin in humans is unclear. Peak night-time concentrations in the plasma are closely associated with the nadirs of core temperature, alertness, performance, and metabolism. The profile of secretion is strongly associated with increasing sleep propensity, and sleep is longer and of better quality when taken in phase with peak melatonin secretion (and with the nadir in core temperature; see Fig. 13.11.3). Melatonin is able to reinforce night-time physiology (e.g. in con- tributing to the propensity to sleep and the decreased nocturnal core temperature). Melatonin appears to play a supporting role in the influence of the light–dark cycle for synchronizing the circadian rhythms to the 24-h day. In the absence of time cues (free-running) the natural period of the human circadian system is on average 24.1 to 24.3 h and the principal resetting agent is light (Fig. 13.11.4). Exogenous melatonin clearly shifts the timing of the internal clock to earlier and later times and synchronizes a free-running clock that is incompletely entrained to the 24-h day (Fig. 13.11.5). Several syn- dromes associated with long-term insomnia in humans appear to result from slower, faster, or free-running sleep–wake cycles. These include the non-24-h sleep–wake cycle of blind people (with no light perception at all), delayed sleep-phase syndrome, advanced sleep-phase syndrome, and irregular sleep–wake cycles. In addition, abrupt shifts of time cues such as are found in shift work and jet lag lead to circadian asynchrony with resultant difficulties affecting sleep, fatigue, and alertness, and with possible long-term health con- sequences. In these circumstances, melatonin has actual and poten- tial therapeutic benefit as a result of its chronobiotic activity. Timed exposure to light at high luminance may improve disorders of the circadian rhythm that affect sleep. However, in many circumstances, the correct timing and intensity of light exposure (and avoidance) is hard to achieve. Notably, blind people cannot have access to light treatment and for the non-24-h sleep–wake disorder of the blind, melatonin, correctly timed, is the treatment of choice. Pharmaceutical use of melatonin In addition to its use in blind circadian rhythm disorder, melatonin has proved successful in normalizing delayed sleep timing in de- layed sleep-phase syndrome, stabilizing irregular sleep–wake cycles in neurologically disabled children, and in treating the symptoms of jet lag. Melatonin treatment has also been suggested as a means to improve sleep in night-shift workers, in older individuals with in- somnia (for which a registered preparation is available on prescrip- tion), and in patients with pineal tumours. Melatonin pg/ml Core body temperature°C Triacylglycerol mmol/litre Alertness 0 = not alert, 100 = very alert Reaction time sec Clock time h Sleep propensity Road accidents 60 40 20 37.1 37.0 36.9 36.8 36.7 36.6 1.8 1.6 1.4 1.2 60 40 20 1.8 1.7 1.6 1.5 1.4 12 16 20 24 04 08 12h Fig. 13.11.3 Relationship of plasma melatonin to other major circadian rhythms. Note the close correspondence between the core temperature nadir and the melatonin peak. Reprinted from The Lancet, Vol. 358, Rajaratnam SM, Arendt J, Health in a 24-h society, Pages 999–1005, Copyright 2001, with permission from Elsevier. Melatonin Free-run Synchronised Biological night (time of daily endogenous melatonin secretion) Time E.g. blindsubjects, Lockley et al., J Endocrinol, 2000 Fig. 13.11.4 Melatonin can synchronize free-running rhythms in both blind and sighted subjects. Before treatment, the subject shows circadian rhythms of melatonin, and sleep which are longer than 24 h.

 Many studies have been carried out to investigate the efficacy of melatonin as a chronobiotic agent for the alleviation of symptoms of jet lag. The results of one meta-analysis to assess the effective- ness of oral melatonin, taken in different dosing regimens for al- leviating jet lag after travel across several time zones, showed that the agent is effective in preventing or reducing jet lag and that its short-term use appears to be safe on an occasional

basis. Side-effect reporting has been low, except in patients with epilepsy or those who are taking warfarin in whom convulsant effects or increased bleeding, respectively, have been reported. Melatonin may theoret- ically influence reproductive development in children and reduce sexual activity, if overused, in adults. No evidence of these effects has yet been reported and the prolonged-release agent has been found to be effective and safe in mitigating the disordered sleep of children with neurodevelopmental diseases. Recent studies of jet lag tend to recommend the use of preflight timed melatonin (0.5 mg) to initiate an advance or delay as required of the circadian system, and to use postflight higher doses (3–5 mg) again timed correctly, to reinforce the shift in timing and to acutely induce sleepiness. Another meta-analysis was less positive. Melatonin is nevertheless recommended as a treatment for jet lag, delayed sleep-phase syn- drome, and irregular sleep–wake cycles by the American Academy of Sleep Medicine. Its use in shift work has proved inconsistent, not all studies have been successful regarding its use in insomnia in older people, and there is insufficient data to evaluate properly its effect in pineal tumours. The timing of treatment with respect to in- ternal circadian timing is very important and judging such timing is often not simple, especially in shift work and jet lag. As a reinforcer of circadian phase melatonin may be useful in other conditions, for example in reduction of blood pressure in pa- tients with essential hypertension. There are increasing associations of melatonin with glucose metabolism and animal data and human genetic studies suggest that either low melatonin secretion or re- duced melatonin signalling can impair insulin sensitivity and lead to type 2 diabetes. However there are considerable controversies in this field. It is likely that any aspect of physiology which depends on per- ception of daylength change, and/or which is driven by the master circadian clock in the suprachiasmatic nucleus (SCN), is susceptible to the effects of melatonin. Melatonin is freely available in the United States of America, and a melatonin formulation has been registered for use in insomnia in older people in Europe. It is available as a prolonged-release prescrip- tion drug (Circadin) and is approved by the European Medicines Agency as a single treatment in a dose of 2 mg for patients aged at least 55 years, for the short-term treatment (up to 13 weeks) of pri- mary insomnia characterized by poor sleep quality. Moreover, the findings of a randomized controlled clinical trial showed that mela- tonin had beneficial effects on delirium in geriatric patients. There is little evidence concerning the advantages or disadvantages of slow as compared to fast release preparations. The European Food Safety Agency (EFSA) Panel on Dietetic Products, Nutrition and Allergies (NDA) considers that reduction of sleep onset latency might be a beneficial physiological effect of mela- tonin (assumed to be a food constituent). The target population is as- sumed to be the general population. The Panel considers that in order to obtain the claimed effect, 1 mg of melatonin should be consumed close to bedtime. It should be noted however that 1 mg melatonin taken or- ally leads to pharmacological, not physiological plasma concentrations in most people, and that the marked circadian dependency of the ef- fects of melatonin is not taken into account by these recommendations. The melatonin MT1/MT2 receptor agonist ramelteon/Rozerem has been approved by the United States Food and Drug Administration (FDA), again for insomnia. The manufacturer Takeda has however withdrawn its application for marketing in Europe. The product re- mains available in the United States and Japan. Most recently the MT1/MT2 receptor agonist tasimelteon (Hetlioz) has been approved for non-24 h sleep–wake disorder in the blind, including paedi- atric use, both by the FDA and in Europe. The manufacturer Vanda 100 75 50 25 12 16 20 0 4 8 12 12 Clock time (h) after mel after plac after mel 100 75 50 25 during mel Sleep efficiency (%) DIRECT EFFECT *

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CIRCADIAN EFFECT 16 20 0 4 8 12 Fig. 13.11.5 Exogenous melatonin has both direct and circadian effects on sleep. Healthy young men (n = 8) received 1.5 mg surge sustained release melatonin (mel) or placebo (plac) in a double-blind cross-over design at 16:00 h daily for 8 days, recumbent, less than 5 lux, 16:00–08:00 h, sleep was evaluated by polysomnography on the night after the last dose of melatonin or placebo and on the subsequent night after melatonin washout. These data confirm the utility of melatonin for the treatment of delayed sleep. In a treatment situation the two effects can be maximized by suitable timing of the dose. Hormones (melatonin, cortisol, TSH) and heart rate variability showed similar substantial phase advances as seen for sleep. From Rajaratnam SMW, Middleton B, Stone BM, Arendt J, Dijk D-J (2004). Melatonin advances the circadian timing of EEG sleep and directly facilitates sleep without altering its duration in extended sleep opportunities in humans. J Physiol, 561, 339–51, by permission. Copyright © 2004, John Wiley and Sons.

13.11 The pineal gland and melatonin 2559 Pharmaceuticals has recognized the important circadian effects of melatonin and its development has targeted circadian disorders and correctly timed treatment. Other formulations and deriva- tives of melatonin are under development and a distinct agonist (agomelatine/Valdoxan) is registered for use in major depression; the potential therapeutic effect is postulated to be mediated by an antag- onist effect on the serotonin receptor, 5HT2C. Its use is constrained by possible hepatic toxicity in patients with liver dysfunction, especially in older people. It is interesting to note that the doses used for all the agonists mentioned are much higher than the recommended doses for melatonin itself. In summary, there is evidence indicating that oral ingestion of melatonin may be beneficial to correct sleep timing, and when used occasionally after transmeridian flights that would induce daytime fatigue and sleep disturbance associated with gastrointestinal complaints, weakness, malaise, loss of mental efficiency, and other symptoms that characterize jet lag. Clearly, since the drug is not as yet licensed in all countries, routine pharmaceutical quality control must be established and the use and safety of melatonin in pregnancy has not yet been completely established. Given that prion-related diseases result from the ingestion or injection of material derived from brain or other animal tissues, only pure biosynthetic melatonin should be considered for human use. Melatonin derived from bovine pineal or other biological sources should be avoided. Recently, partial deficiency of melatonin, induced by excess noc- turnal exposure to light, has been suggested to explain an increased risk of cancer in shift workers. It seems more likely that a general dis-turbance of the circadian system rather than selective suppression of melatonin provides the mechanistic explanation for the increased frequency of cancers in this group. Melatonin also has antioxidant properties and is widely taken in certain communities, particularly in the United States of America, where it is claimed to provide un- specified protection against ageing, degenerative diseases, cancer, and impaired immune function, as well as reproductive and psychi- atric illness. Nonetheless, it should be acknowledged that, as in other vertebrates, melatonin has diverse physiological actions in humans, many of which are not fully understood. At present, the principal authenticated indication for exogenous melatonin is for the control of sleep disorders in adults, in children with neurodevelopmental abnormalities, and the treatment of symptoms associated with jet lag, rather than the many conditions for which our scientific under- standing of its proposed benefits is as yet incomplete. FURTHER READING Al-Aama T, et al. (2011). Melatonin decreases delirium in elderly patients: a randomized, placebo-controlled trial. Int J Geriatr Psychiatry, 26, 687–94. Arendt J (1995). Melatonin and the mammalian pineal gland. Chapman & Hall, London. Arendt J (2000). Melatonin, circadian rhythms, and sleep. N Engl J Med, 343, 1114–6. Arendt J

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