The **pineal gland** is a neuroendocrine organ located in the midline of the brain. Melatonin, thought to be the output hormone of the pineal gland, plays a central role in the co-ordination of circadian rhythms and the circadian system.

**Circadian rhythms** are centrally co-ordinated and physiological, psychological and behavioural processes, which in humans follow approximately a 24- to 25-hour alternating cycle. In humans, circadian rhythms are genetically programmed to synchronise with night and day.

Over a period of ten years there has been an expansion of interest in circadian systems, how their disruption impacts on health and how they can be manipulated to improve health and optimise treatment.

## The circadian system

The circadian system consists of a central ‘biological master clock’ (located in the suprachiasmatic nucleus (SCN) of the hypothalamus) and peripherally located biological clocks (found in most tissues such as the heart and liver).

This system has an endogenous rhythmicity of approximately 24 hours. Peripheral ‘clocks’ can work independently of the external light/dark cycle but are synchronised by the ‘master clock’ in the SCN of the hypothalamus. Physiological cues from the SCN entrain or reset the peripheral clocks, and the master clock responds to external cues such as the light/dark cycle, exercise and nutrient intake.

The system creates a biological night and a biological day so that:

- Physiological and behavioural activities best suited for night time (such as rest, memory processing, cellular repair and brain development) take place at night.
- Those activities best suited for daytime (such as alertness and the availability of glucose, take place during the day. The prolonged disruption of the circadian synchrony leads to an array of disorders, including insomnias, impaired glucose tolerance and obesity and decreased life expectancy.

### Synchronisation of the circadian system

The biological clock within the SCN is thought to be the pacemaker of the circadian system, since lesions to the SCN alter circadian physiology and behaviour. The SCN co-ordinates circadian rhythms via endocrine and neural pathways. These include melatonin, the renin-angiotensin system, the hypothalamic-pituitary-adrenal axis including cortisol, and the hypothalamic-pituitary-thyroid axis and adrenaline (epinephrine). Animal studies have revealed neurological connections of the SCN to the pineal gland, heart, kidneys, adrenal cortex, liver, pancreas, spleen and white and brown adipose tissue.

**How is the circadian system synchronised with night and day?**

Circadian clocks communicate with, and can be ‘reset’ or entrained by, our external environment via photic and non-photic signals such as melatonin, feeding and exercise. Light is, however, the most potent ‘Zeitgeber’ (‘time giver’), or cue, for the SCN.

The ‘master clock’ in the SCN is affected by light and darkness via the retino-hypothalamic tract, which connects the retinal ganglion cells (RGCs) of the retinae to the SCN in the hypothalamus. This connects with the pineal gland via the superior cervical ganglion (SCG).

Sunlight (or light at 480 nm) stimulates the RGCs to produce the photoreceptor melanopsin. Melanopsin ‘signals’ daytime to the SCN, which in turn induces the pineal gland to suppress melatonin production.

**RGCs → melanopsin → SCN → SCG → pineal gland → melatonin supression**

In the absence of light or melanopsin, melatonin is produced by the pineal gland. In humans, it induces an almost irresistible urge to sleep. Its primary function is to signal day length to the SCN so that it can synchronise the day/night cycle with:

- Endocrine rhythms
- Body temperature
- Glucose homeostasis
- Lipogenesis
- Locomotor activity

### Disruption of the circadian system
It can occur as a result of external factors of conditions such as light at night during shift work or crossing meridian time zones (jet lag), genetic predisposition or abnormalities which affect the functioning of the retino-hypothalamic system, the production of melatonin, or the sensitivity of the system to light (for example, seasonal affective disorder (SAD)), physical damage or tumours of the pineal gland or the SCN.

- **Age and ageing:** the pineal gland is large in children but shrinks at puberty and has diminished activity in the elderly.
- **Jet lag, shift work and exposure to bright light at night:** these result in desynchrony between the internal clock and the external light-dark cycle brought on by rapid travel across time zones or by working a non-standard schedule.[2]
- **Genetic aberrations to ‘clock’ genes:** for example, in SAD and possibly in rheumatoid arthritis.
- **Tumours or lesions to the SCN or pineal gland:** there has been a continuous interest in the use of melatonin as a marker for neoplasms of the pineal region. Melatonin decreases following pinealectomy and can cause alterations in the sleep/wake cycle. However, because these tumours are extremely rare, it has been difficult to find conclusive evidence for the effect of pineal tumours on circadian rhythms.[3]
- **Damage to the retino-hypothalamic tract or pineal gland:** severely sight impaired people with no conscious or unconscious light perception frequently display free-running rhythms.

**Changes of the pineal gland with age[4]**

The pineal gland is large in children but shrinks at puberty; however, the roles of the pineal gland and melatonin in human pubertal development remain unclear.

Treatment of children with sleep disorders with melatonin for an average of three years was not found to be associated with alterations in pubertal development in children[5]. However, there is a report in the literature of juvenile hamartoma of the pineal gland being associated with melatonin deficiency and precocious puberty[6].

The activity of the pineal gland declines with advancing age:

- Elderly people with sleep disturbance have impaired melatonin production compared with age-matched controls.
- Campaigns aiming to reduce the use of benzodiazepines failed when they were not associated with the availability and market uptake of prolonged-release (PR) melatonin. The reimbursement of PR melatonin supports better penetration rates and a higher reduction in sales for benzodiazepine drugs[7].
- In one study, outpatients with mild cognitive impairment exhibited significant improvements in cognitive function, sleep profiles and depression compared with those given placebo[8].
- Sundown syndrome - characterised by agitation, confusion, aggressiveness and anxiety occurring in the late afternoon in patients with dementia. It is thought to be due in part to impaired circadian rhythmicity and is associated with degeneration in the SCN[9]. Reduced melatonin levels are seen in several neurodegenerative disorders, including Alzheimer's disease and Pick's disease[10].

Jet lag, shift work and exposure to bright light at night

These can result in desynchrony between the internal clock and the external light-dark cycle (brought on by rapid travel across time zones or by working a non-standard schedule) and reduce melatonin levels.

Short-term exposure can result in sleep disorders, gastrointestinal symptoms, poor concentration and irritability. Long-term exposure, however, has been associated with an increased risk of cancers, cardiovascular disorders and diabetes.

**Short-term treatment of jet lag[2]**

Short-term, intermittent jet lag symptoms can be avoided by manipulating the circadian system's ability to be reset or entrained by bright light, melatonin, exercise, or the use of sleeping agents or stimulants.

**Bright light therapy for jet lag**

- The human core temperature tends to dip to its lowest point 2-3 hours before we are due to wake up.
- Exposure to bright light before this dip causes a phase delay, and encourages later sleep (desirable for westward travel across time zones).
- Exposure to bright light after this dip causes a phase advance, and encourages sleep earlier than usual (desirable for eastward travel across time zones).
- Exposure to bright light can be avoided by wearing dark glasses or by remaining in a darkened room.
- In order to avoid inadvertently phase advancing or delaying, web tools can be used to aid travellers to optimise light exposure or avoidance to prevent jet lag[11].

Melatonin for jet lag

- Melatonin is indicated for travel across more than five time zones but may be used in those travelling across two to four time zones if needed.
- 0.5 mg of melatonin is equally as effective as 5 mg, although 5 mg results in quicker, more effective sleep. More than 5 mg is not more effective than 5 mg.
- Timing of melatonin is essential in order to optimise its effects - taking it earlier in the day induces drowsiness and delays effective sleep at night.
In travellers crossing seven to eight time zones the administration of melatonin on arrival at the destination area is enough; however, when more time zones are crossed, melatonin should be administered for two to three days before the flight, its hypnotic and sedative action being appropriately managed.

Hypnotics for jet lag

- The use of hypnotics in the treatment of jet lag is common but poorly researched.
- They appear to be effective in improving sleep in patients with jet lag; however, their effects on other symptoms are unknown.
- Data comparing the effects of melatonin and hypnotics (zolpidem) for jet lag are equivocal; however, melatonin has fewer side-effects.

Stimulants and jet lag

- Stimulant medications such as caffeine 300 mg or modafinil may improve sleepiness associated with jet lag but they may be associated with more nocturnal sleep complaints.

Reducing circadian disruption for long-term shift workers

- Fewer than 3% of permanent night workers show complete adaptation of their circadian system to their imposed work schedule and fewer than 25% adjust to a point that some benefit would be derived from the adaptive shift that they have made.
- Partial re-entrainment to a permanent night shift schedule, with the following activities, is associated with greatly reduced impairment of the circadian rhythm during night shifts:
  - Intermittent bright light pulses during night shifts.
  - Wearing dark sunglasses outside.
  - Scheduled sleep episodes in darkness.

- In one study of rotating shift-work female nurses with clinical insomnia, higher intensity and briefer duration of bright light exposure during the first half of their evening/night shift, with a daytime darkness procedure, improved their insomnia, anxiety and depression.
- Circadian realignment has not yet been associated with a reduction in the long-term effects of shift work.

Consequences of prolonged circadian disruption

Cancer

- A reduction in melatonin level is associated with a number of tumours, including prostate, endometrial and breast cancers. The reason for this is unclear.
- In 2007, the International Agency for Research on Cancer classified shift work that involves circadian disruption "as a probable carcinogen". However, to date this has not been conclusively proved by epidemiological studies. A meta-analysis found that night-shift work had little or no effect in the incidence of breast cancer in women.
- Abberations in clock genes affecting the action of melatonin in various tissues have been associated with cancers (for example, non-Hodgkin's lymphoma).
- Melatonin inhibits human cancer cell growth in cultures and has been shown to exert oncostatic activity by antiproliferative actions, stimulation of anticancer immunity, modulation of oncogene expression and anti-inflammatory, antioxidant and anti-angiogenic activity.
- The administration of melatonin alone or in combination with aldesleukin (interleukin-2) in conjunction with chemoradiotherapy and/or supportive care in cancer patients with advanced solid tumours, has been associated with improved outcomes of tumour regression and survival.
- Chemotherapy has been shown to be better tolerated in patients treated with melatonin.

Hypertension and cardiovascular disease

- In healthy individuals, there is a circadian variation of BP with a nocturnal fall of 10-20% during the sleep period.
- In hypertensive patients, this circadian rhythm may disappear or even become inverted. Patients have been classified as:
  - 'Dippers' when the mean night-time BP is ≥10% lower than the mean daytime BP
  - 'Non-dippers' when the reduction is <10%
  - 'Risers' when it is higher

- Non-dippers and risers are at an increased risk for target organ damage and cardiovascular events. Non-dippers have been found to have lower melatonin levels at night.
- The renin angiotensin system (RAS) is considered to be the most important endocrine regulator of cardiovascular homeostasis.
- Pineal RAS modulates the synthesis of melatonin.
- Accumulating evidence suggests that angiotensin not only interferes with melatonin synthesis and release but also that both hormones interact at several levels, having opposing effects in cardiovascular and metabolic pathophysiology.

Circadian rhythms and antihypertensive treatment

- Melatonin: PR melatonin improves nocturnal BP.
- **Chronotherapy (timing of BP therapy)**: among patients with a non-dipping BP profile, a once-daily evening (in comparison to morning) ingestion schedule of the angiotensin-II receptor antagonists (AIIRAs) irbesartan, olmesartan, telmisartan, and valsartan, exerted a greater therapeutic effect on nocturnal BP, with normalisation of the circadian BP profile toward a more dipping pattern.

**Melatonin and ischaemic heart disease**
One study reported an association between lower melatonin levels and myocardial infarction in women with high BMI[22].
Insulin and metabolic syndrome [23]
The interaction between melatonin, circadian rhythms and the RAS has also been implicated in the pathophysiology of type II diabetes and metabolic syndrome. There is accumulating evidence that the RAS plays a major role in the development of dyslipidaemias, in altered glucose homeostasis and in hypertension of the metabolic syndrome.

- Angiotensin II causes insulin resistance through activation of angiotensin receptors and increased production of mineralocorticoid.
- Treatment with ARIs and angiotensin-converting enzyme (ACE) inhibitors has beneficial effects in patients with diabetes.
- The underlying mechanisms through which it does this remain unknown.
- Lower melatonin secretion has been independently associated with an increased risk of developing type 2 diabetes.

Mental health [24]
Seasonal affective disorder (SAD) [25]
SAD is a subtype of depression, which characteristically occurs during the winter months and is more common in northern latitudes:

- It is associated with genetic aberrations which cause abnormalities along the retino-hypothalamic tract.
- It is thought that these lead to a ‘phase shift’ in the circadian cycle, which worsens as sunlight hours reduce.
- However, the evidence supporting the use of melatonin in the prevention and treatment of SAD is equivocal.
- Likewise, the newer antidepressant drug, agomelatine, which combines melatonergic and serotonergic activity, has been associated with positive outcomes for this disorder; however, further research is needed.

Other mental health disorders [6]
- Melatonin levels at night have been found to be decreased in patients with depression and dysthymia and increased in those with mania.
- Treatment with melatonin has not been found to improve defining features of these disorders but helps to improve the insomnia associated with it.

Rheumatoid arthritis [26]
Patients with rheumatoid arthritis have disturbances in the hypothalamic-pituitary-adrenal axis. These are reflected in altered circadian rhythm of circulating serum cortisol, melatonin and interleukin-6 (IL-6) levels and in chronic fatigue.

Timing of medications for rheumatoid arthritis according to these changes has been associated with beneficial treatment effects.

Further reading & references


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